# 1. Gene Aliases

Jun Proto-Oncogene AP-1 Transcription Factor Subunit, V-Jun Avian Sarcoma Virus 17 Oncogene Homolog, AP-1, Transcription Factor AP-1 Subunit Jun, Transcription Factor Jun, Proto-Oncogene C-Jun, Activator Protein 1, Jun Oncogene, C-Jun, AP1, P39, V-Jun Sarcoma Virus 17 Oncogene Homolog, Jun Activation Domain Binding Protein, Enhancer-Binding Protein AP1, Transcription Factor AP-1, Proto-Oncogene CJun, C-JUN, CJUN.

[<https://www.genecards.org/cgi-bin/carddisp.pl?gene=JUN&keywords=Jun#aliases_descriptions>]

# 2. Association with Toxicity and/or Disease at a Transcriptional Level

* UV irradiation of skin activates c-Jun through JNK1 signaling pathway [PMID: 9525748], which induce c-Jun phosphorylation [PMID: 11180173].
* Inducible epidermal deletion of JunB and c-Jun in adult mice leads to psoriasis-like skin disease, including arthritic lesions [PMID: 16163348].

# 3. Summary of Protein Family and Structure

* Protein Accession: P05412
* Size: 331 amino acids
* Molecular mass: 35676 Da
* Domains: bZIP, bZIP\_sf, JNK, Leuzip\_Jun, TF\_DNA-bd\_sf
* Blocks: bZIP transcription factor, bZIP\_1 Jun transcription factor signature, Jun-like transcription factor
* Family: Belongs to the bZIP family. Jun subfamily
* Jun is a transcription factor that recognizes and binds to the AP-1 consensus motif 5’-TGA[GC]TCA-3’ [PMID: 22083952]. The AP-1 transcription factors is a collective term for dimers formed by proteins of the Jun, Fos, activating transcription factor (ATF) and musculoaponeurotic fibrosarcoma (MAF) families. These are structurally similar and functionally related basic leucine zipper (bZIP) proteins, which form homo- and/or hetero-dimers through the bZIP domain. Dimerization brings together the basic regions, producing a contiguous DNA-contact interface that interacts with specific sequences of DNA. Once bound to DNA, the AP-1 complexes function as transcription regulators to either activate or repress target gene transcription.
* Jun can form homo- or hetero-dimers with members of Fos families, and c-Maf and Nrl. Jun/ATF preferentially binds to the cAMP-responsive element (CRE, 5’-TGACGTCA-3’), while Jun/Fos has high affinity for the phorbol 12 O-tetradecanoate-13-acetate (TPA)-responsive element (TRE, 5’-TGAG/CTCA-3’) [PMID: 22180088]
* Jun can also interact with proteins outside of AP-1 family. Examples for this type of interaction include c-Jun binding to the Ets domain of PU.1, directing the complex to the PU.1 binding site in the M-CSF receptor promoter for transcriptional activation [PMID: 9988737], whereas, the c-Jun/MyoD complex is recruited to the MyoD promoter to inhibit myogenesis [PMID: 1310896].
* c-Jun is essential for mouse embryonic development and also for normal cell proliferation, since c-Jun-deficient mouse embryo fibroblasts (MEFs) exhibit a profound senescence-like growth arrest in culture [PMID: 8330736].
* Glycogen synthase kinase 3 (GSK-3) and CKII can phosphorylate c-Jun at its C-termini, keeping c-Jun in a non DNA-binding state [PMID: 1846781], while extracellular signal regulated kinase (ERK) can activate p70 S6 kinase, which in turn phosphorylates GSK-3 at serine-21, resulting in its inactivation [PMID: 7806638]. Hence, ERK, by acting through the p70 S6 kinase-GSK-3 cascades, causes c-Jun C-terminal dephosphorylation and increases its DNA binding activity.
* The c-Jun amino-terminal kinases (JNKs) phosphorylate c-Jun at the N-terminal domain at serines 63 and 73, the phosphorylation requires binding of JNK to a specific region within the c-Jun transactivation domain [PMID: 8177321]. Activation of JNKs is a result of MAP3K-MAP2K-MAPK signaling pathway, where MAP3K kinases activate MEK1 and MEK2 which in turn phosphorylate JNK [PMID: 19629069].
* Functional analysis reveals three c-JUN phosphorylation states: unphosphorylated c-JUN recruits the MBD3 repressor, serine63/73 doubly-phosphorylated c-JUN binds to the TCF4 co-activator, whereas the fully phosphorylated form disfavours TCF4 binding attenuating JNK signalling [PMID: 36253406].
* Sporothrix schenckii regulates macrophage inflammatory responses via the c-JUN-induced Dab2 transcription in sporotrichosis-induced skin lesions in mice [PMID: 35441732].
* Transcriptional repression of c-Jun’s E3 ubiquitin ligases contributes to c-Jun induction by UV [PMID: 18295447].

# 4. Proteins Known to Interact with Gene Product

## Interactions with experimental support

* **MAPK8** Mitogen-activated protein kinase 8; Serine/threonine-protein kinase involved in various processes such as cell proliferation, differentiation, migration, transformation and programmed cell death. Extracellular stimuli such as proinflammatory cytokines or physical stress stimulate the stress- activated protein kinase/c-Jun N-terminal kinase (SAP/JNK) signaling pathway. In this cascade, two dual specificity kinases MAP2K4/MKK4 and MAP2K7/MKK7 phosphorylate and activate MAPK8/JNK1. [PMID: 10101227, PMID: 10393177, PMID: 10398438, PMID: 10419510, PMID: 10464310]
* **FOS** Proto-oncogene c-Fos; Nuclear phosphoprotein which forms a tight but non-covalently linked complex with the JUN/AP-1 transcription factor. In the heterodimer, FOS and JUN/AP-1 basic regions each seems to interact with symmetrical DNA half sites. On TGF-beta activation, forms a multimeric SMAD3/SMAD4/JUN/FOS complex at the AP1/SMAD-binding site to regulate TGF-beta-mediated signaling. Has a critical function in regulating the development of cells destined to form and maintain the skeleton. [PMID: 10488148, PMID: 11053448, PMID: 11090181, PMID: 11431474, PMID: 15319445, PMID: 15718494, PMID: 15867431, PMID: 15994313, PMID: 16008525, PMID: 16055710, PMID: 1631061, PMID: 16511568, PMID: 16714286, PMID: 16928824, PMID: 17440114, PMID: 18172215, PMID: 18535250]
* **JUN** Transcription factor AP-1; Transcription factor that recognizes and binds to the enhancer heptamer motif 5’-TGA[CG]TCA-3’. Promotes activity of NR5A1 when phosphorylated by HIPK3 leading to increased steroidogenic gene expression upon cAMP signaling pathway stimulation. Involved in activated KRAS-mediated transcriptional activation of USP28 in colorectal cancer (CRC) cells. Binds to the USP28 promoter in colorectal cancer (CRC) cells. Belongs to the bZIP family. Jun subfamily. [PMID: 10488148, PMID: 11278640, PMID: 12080089, PMID: 1631061, PMID: 16511568, PMID: 20102225, PMID: 21675959, PMID: 25609649, PMID: 7848298, PMID: 8440710, PMID: 8662824, PMID: 10488148, PMID: 11278640, PMID: 12080089, PMID: 1631061, PMID: 16511568, PMID: 20102225, PMID: 21675959, PMID: 25609649, PMID: 7848298, PMID: 8440710, PMID: 8662824]
* **MAPK9** Mitogen-activated protein kinase 9; Serine/threonine-protein kinase involved in various processes such as cell proliferation, differentiation, migration, transformation and programmed cell death. Extracellular stimuli such as proinflammatory cytokines or physical stress stimulate the stress- activated protein kinase/c-Jun N-terminal kinase (SAP/JNK) signaling pathway. In this cascade, two dual specificity kinases MAP2K4/MKK4 and MAP2K7/MKK7 phosphorylate and activate MAPK9/JNK2. [PMID: 10490605, PMID: 11278395, PMID: 12788955, PMID: 15637069, PMID: 16533805, PMID: 16824735, PMID: 17189706, PMID: 17875713, PMID: 18940813, PMID: 1922387, PMID: 19527717, PMID: 19910486, PMID: 8001819, PMID: 8654373, PMID: 8945519, PMID: 8985011, PMID: 9405416, PMID: 9596579]
* **ATF2** Cyclic AMP-dependent transcription factor ATF-2; Transcriptional activator which regulates the transcription of various genes, including those involved in anti-apoptosis, cell growth, and DNA damage response. Dependent on its binding partner, binds to CRE (cAMP response element) consensus sequences (5’-TGACGTCA- 3’) or to AP-1 (activator protein 1) consensus sequences (5’-TGACTCA- 3’). In the nucleus, contributes to global transcription and the DNA damage response, in addition to specific transcriptional activities that are related to cell development, proliferation and death. [PMID: 10207054, PMID: 10327051, PMID: 15546613, PMID: 16511568, PMID: 1827203, PMID: 18641343, PMID: 20102225, PMID: 20195357, PMID: 20511396, PMID: 2320002, PMID: 23661758, PMID: 25609649, PMID: 26496610, PMID: 28514442, PMID: 31515488, PMID: 8027667, PMID: 9445037]
* **EP300** Histone acetyltransferase p300; Functions as histone acetyltransferase and regulates transcription via chromatin remodeling. Acetylates all four core histones in nucleosomes. Histone acetylation gives an epigenetic tag for transcriptional activation. Mediates cAMP-gene regulation by binding specifically to phosphorylated CREB protein. Mediates acetylation of histone H3 at ‘Lys-122’ (H3K122ac), a modification that localizes at the surface of the histone octamer and stimulates transcription, possibly by promoting nucleosome instability. [PMID: 10327051, PMID: 11689449, PMID: 11980644, PMID: 12437352, PMID: 12471036, PMID: 14630807, PMID: 21268080, PMID: 21937452, PMID: 24069158, PMID: 24636898, PMID: 27956703]
* **ATF3** Cyclic AMP-dependent transcription factor ATF-3; This protein binds the cAMP response element (CRE) (consensus: 5’-GTGACGT[AC][AG]-3’), a sequence present in many viral and cellular promoters. Represses transcription from promoters with ATF sites. It may repress transcription by stabilizing the binding of inhibitory cofactors at the promoter. Isoform 2 activates transcription presumably by sequestering inhibitory cofactors away from the promoters. [PMID: 10327051, PMID: 14667575, PMID: 1827203, PMID: 20102225, PMID: 20304822, PMID: 23661758, PMID: 25609649, PMID: 26496610, PMID: 8622660, PMID: 8649793]
* **CREBBP** CREB-binding protein; Acetylates histones, giving a specific tag for transcriptional activation. Also acetylates non- histone proteins, like DDX21, FBL, IRF2, MAFG, NCOA3, POLR1E/PAF53 and FOXO1. Binds specifically to phosphorylated CREB and enhances its transcriptional activity toward cAMP-responsive genes. Acts as a coactivator of ALX1. Acts as a circadian transcriptional coactivator which enhances the activity of the circadian transcriptional activators: NPAS2-ARNTL/BMAL1 and CLOCK-ARNTL/BMAL1 heterodimers. [PMID: 10327051, PMID: 15994313, PMID: 16055710, PMID: 17296604, PMID: 18443043, PMID: 2138276, PMID: 8028671, PMID: 9659924, PMID: 9786917]
* **FOSL1** Fos-related antigen 1; FOS like 1, AP-1 transcription factor subunit; Belongs to the bZIP family. Fos subfamily. [PMID: 11431474, PMID: 11708771, PMID: 11912197, PMID: 20511396, PMID: 23661758, PMID: 24029232, PMID: 26258633, PMID: 9160889]
* **FOSL2** Fos-related antigen 2; Controls osteoclast survival and size. As a dimer with JUN, activates LIF transcription. Activates CEBPB transcription in PGE2- activated osteoblasts. [PMID: 11708771, PMID: 20102225, PMID: 25609649, PMID: 26186194, PMID: 26496610, PMID: 28514442, PMID: 32296183, PMID: 9160889]
* **COP1** E3 ubiquitin-protein ligase COP1; E3 ubiquitin-protein ligase that mediates ubiquitination and subsequent proteasomal degradation of target proteins. E3 ubiquitin ligases accept ubiquitin from an E2 ubiquitin-conjugating enzyme in the form of a thioester and then directly transfers the ubiquitin to targeted substrates. Involved in JUN ubiquitination and degradation. Directly involved in p53 (TP53) ubiquitination and degradation, thereby abolishing p53-dependent transcription and apoptosis. Ubiquitinates p53 independently of MDM2 or RCHY1. [PMID: 12615916, PMID: 14739464, PMID: 15994960, PMID: 25117710, PMID: 25609649, PMID: 27534417, PMID: 28514442, PMID: 31155351]
* **FBXW7** F-box/WD repeat-containing protein 7; Substrate recognition component of a SCF (SKP1-CUL1-F-box protein) E3 ubiquitin-protein ligase complex which mediates the ubiquitination and subsequent proteasomal degradation of target proteins. Recognizes and binds phosphorylated sites/phosphodegrons within target proteins and thereafter bring them to the SCF complex for ubiquitination. Identified substrates include cyclin-E (CCNE1 or CCNE2), DISC1, JUN, MYC, NOTCH1 released notch intracellular domain (NICD), NOTCH2, MCL1, and probably PSEN1. [PMID: 14739463, PMID: 16023596, PMID: 28036276, PMID: 29225075, PMID: 29346117, PMID: 30044990, PMID: 31843895]
* **NFE2L2** Nuclear factor erythroid 2-related factor 2; Transcription factor that plays a key role in the response to oxidative stress: binds to antioxidant response (ARE) elements present in the promoter region of many cytoprotective genes, such as phase 2 detoxifying enzymes, and promotes their expression, thereby neutralizing reactive electrophiles. In normal conditions, ubiquitinated and degraded in the cytoplasm by the BCR(KEAP1) complex. [PMID: 12805554, PMID: 19666106, PMID: 20194533, PMID: 20232342, PMID: 32911434, PMID: 9872330]
* **CREB5** Cyclic AMP-responsive element-binding protein 5; Binds to the cAMP response element and activates transcription. [PMID: 25609649, PMID: 26186194, PMID: 26496610, PMID: 28514442, PMID: 8440710]
* **SMAD3** Mothers against decapentaplegic homolog 3; Receptor-regulated SMAD (R-SMAD) that is an intracellular signal transducer and transcriptional modulator activated by TGF-beta (transforming growth factor) and activin type 1 receptor kinases. Binds the TRE element in the promoter region of many genes that are regulated by TGF-beta and, on formation of the SMAD3/SMAD4 complex, activates transcription. Also can form a SMAD3/SMAD4/JUN/FOS complex at the AP- 1/SMAD site to regulate TGF-beta-mediated transcription. [PMID: 10220381, PMID: 10903323, PMID: 11306568, PMID: 21829441, PMID: 9732876]
* **BATF3** Basic leucine zipper transcriptional factor ATF-like 3; AP-1 family transcription factor that controls the differentiation of CD8(+) thymic conventional dendritic cells in the immune system. Required for development of CD8-alpha(+) classical dendritic cells (cDCs) and related CD103(+) dendritic cells that cross- present antigens to CD8 T-cells and produce interleukin-12 (IL12) in response to pathogens (By similarity). Acts via the formation of a heterodimer with JUN family proteins that recognizes and binds DNA sequence 5’-TGA[CG]TCA-3’ and regulates expression of target genes. [PMID: 10878360, PMID: 20102225, PMID: 23661758, PMID: 25609649, PMID: 28514442]
* **MAPK1** Mitogen-activated protein kinase 1; Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements. [PMID: 10419510, PMID: 11431474, PMID: 1922387, PMID: 25609649, PMID: 29225075]
* **SP1** Transcription factor Sp1; Transcription factor that can activate or repress transcription in response to physiological and pathological stimuli. Binds with high affinity to GC-rich motifs and regulates the expression of a large number of genes involved in a variety of processes such as cell growth, apoptosis, differentiation and immune responses. Highly regulated by post-translational modifications (phosphorylations, sumoylation, proteolytic cleavage, glycosylation and acetylation). Binds also the PDGFR-alpha G-box promoter. [PMID: 10506225, PMID: 16478997, PMID: 17215518, PMID: 25879517]
* **MYC** Myc proto-oncogene protein; Transcription factor that binds DNA in a non-specific manner, yet also specifically recognizes the core sequence 5’-CAC[GA]TG-3’. Activates the transcription of growth-related genes. Binds to the VEGFA promoter, promoting VEGFA production and subsequent sprouting angiogenesis. Regulator of somatic reprogramming, controls self-renewal of embryonic stem cells. Functions with TAF6L to activate target gene expression through RNA polymerase II pause release (By similarity). [PMID: 20232342, PMID: 21150319, PMID: 22266862, PMID: 25303530]
* **ATF4** Cyclic AMP-dependent transcription factor ATF-4; Transcriptional activator. Binds the cAMP response element (CRE) (consensus: 5’-GTGACGT[AC][AG]-3’), a sequence present in many viral and cellular promoters. Cooperates with FOXO1 in osteoblasts to regulate glucose homeostasis through suppression of beta-cell production and decrease in insulin production (By similarity). It binds to a Tax-responsive enhancer element in the long terminal repeat of HTLV-I. Regulates the induction of DDIT3/CHOP and asparagine synthetase (ASNS) in response to endoplasmic reticulum (ER) stress. [PMID: 1827203, PMID: 20936779, PMID: 23661758, PMID: 25241761]
* **SIRT1** NAD-dependent protein deacetylase sirtuin-1; NAD-dependent protein deacetylase that links transcriptional regulation directly to intracellular energetics and participates in the coordination of several separated cellular functions such as cell cycle, response to DNA damage, metabolism, apoptosis and autophagy. Can modulate chromatin function through deacetylation of histones and can promote alterations in the methylation of histones and DNA, leading to transcriptional repression. [PMID: 18823944, PMID: 20042607, PMID: 23382074, PMID: 25609649]
* **SMAD2** Mothers against decapentaplegic homolog 2; Receptor-regulated SMAD (R-SMAD) that is an intracellular signal transducer and transcriptional modulator activated by TGF-beta (transforming growth factor) and activin type 1 receptor kinases. Binds the TRE element in the promoter region of many genes that are regulated by TGF-beta and, on formation of the SMAD2/SMAD4 complex, activates transcription. May act as a tumor suppressor in colorectal carcinoma. Positively regulates PDPK1 kinase activity by stimulating its dissociation from the 14-3-3 protein YWHAQ which acts as a negative regulator. [PMID: 10220381, PMID: 11371641, PMID: 20195357, PMID: 25609649]
* **UBC** Polyubiquitin-C; [Ubiquitin]: Exists either covalently attached to another protein, or free (unanchored). When covalently bound, it is conjugated to target proteins via an isopeptide bond either as a monomer (monoubiquitin), a polymer linked via different Lys residues of the ubiquitin (polyubiquitin chains) or a linear polymer linked via the initiator Met of the ubiquitin (linear polyubiquitin chains). [PMID: 15469925, PMID: 17592138, PMID: 19343052, PMID: 20936779]
* **COPS5** COP9 signalosome complex subunit 5; Probable protease subunit of the COP9 signalosome complex (CSN), a complex involved in various cellular and developmental processes. The CSN complex is an essential regulator of the ubiquitin (Ubl) conjugation pathway by mediating the deneddylation of the cullin subunits of the SCF-type E3 ligase complexes, leading to decrease the Ubl ligase activity of SCF-type complexes such as SCF, CSA or DDB2. [PMID: 10766246, PMID: 20093369, PMID: 25609649, PMID: 8837781]
* **CSNK2A1** Casein kinase II subunit alpha; Catalytic subunit of a constitutively active serine/threonine-protein kinase complex that phosphorylates a large number of substrates containing acidic residues C-terminal to the phosphorylated serine or threonine. Regulates numerous cellular processes, such as cell cycle progression, apoptosis and transcription, as well as viral infection. May act as a regulatory node which integrates and coordinates numerous signals leading to an appropriate cellular response. [PMID: 12628923, PMID: 1516134, PMID: 25609649, PMID: 9685505]
* **PML** Protein PML; Functions via its association with PML-nuclear bodies (PML- NBs) in a wide range of important cellular processes, including tumor suppression, transcriptional regulation, apoptosis, senescence, DNA damage response, and viral defense mechanisms. Acts as the scaffold of PML-NBs allowing other proteins to shuttle in and out, a process which is regulated by SUMO-mediated modifications and interactions. [PMID: 10620019, PMID: 15626733, PMID: 16916642, PMID: 9671405]
* **ITCH** E3 ubiquitin-protein ligase Itchy homolog; Acts as an E3 ubiquitin-protein ligase which accepts ubiquitin from an E2 ubiquitin-conjugating enzyme in the form of a thioester and then directly transfers the ubiquitin to targeted substrates. Catalyzes ‘Lys-29’-, ‘Lys-48’- and ‘Lys-63’-linked ubiquitin conjugation. Involved in the control of inflammatory signaling pathways. Essential component of a ubiquitin-editing protein complex, comprising also TNFAIP3, TAX1BP1 and RNF11, that ensures the transient nature of inflammatory signaling pathways. [PMID: 16901904, PMID: 17110928, PMID: 19806201, PMID: 19818398]
* **DACH1** Dachshund homolog 1; Transcription factor that is involved in regulation of organogenesis. Seems to be a regulator of SIX1, SIX6 and probably SIX5. Corepression of precursor cell proliferation in myoblasts by SIX1 is switched to coactivation through recruitment of EYA3 to the SIX1-DACH1 complex. Transcriptional activation seems also to involve association of CREBBP. Seems to act as a corepressor of SIX6 in regulating proliferation by directly repressing cyclin-dependent kinase inhibitors, including the p27Kip1 promoter (By similarity). [PMID: 16980615, PMID: 17182846, PMID: 25609649]
* **UBB** Polyubiquitin-B; [Ubiquitin]: Exists either covalently attached to another protein, or free (unanchored). When covalently bound, it is conjugated to target proteins via an isopeptide bond either as a monomer (monoubiquitin), a polymer linked via different Lys residues of the ubiquitin (polyubiquitin chains) or a linear polymer linked via the initiator Met of the ubiquitin (linear polyubiquitin chains). [PMID: 16023596, PMID: 17592138, PMID: 8087846]
* **NCOA1** Nuclear receptor coactivator 1; Nuclear receptor coactivator that directly binds nuclear receptors and stimulates the transcriptional activities in a hormone- dependent fashion. Involved in the coactivation of different nuclear receptors, such as for steroids (PGR, GR and ER), retinoids (RXRs), thyroid hormone (TRs) and prostanoids (PPARs). Also involved in coactivation mediated by STAT3, STAT5A, STAT5B and STAT6 transcription factors. Displays histone acetyltransferase activity toward H3 and H4; the relevance of such activity remains however unclear. [PMID: 10567404, PMID: 10847592, PMID: 9642216]
* **SPI1** Transcription factor PU.1; Binds to the PU-box, a purine-rich DNA sequence (5’-GAGGAA- 3’) that can act as a lymphoid-specific enhancer. This protein is a transcriptional activator that may be specifically involved in the differentiation or activation of macrophages or B-cells. Also binds RNA and may modulate pre-mRNA splicing (By similarity); Belongs to the ETS family. [PMID: 10411939, PMID: 12091339, PMID: 9681824]
* **ARIH1** E3 ubiquitin-protein ligase ARIH1; E3 ubiquitin-protein ligase, which catalyzes ubiquitination of target proteins together with ubiquitin-conjugating enzyme E2 UBE2L3. Acts as an atypical E3 ubiquitin-protein ligase by working together with cullin-RING ubiquitin ligase (CRL) complexes and initiating ubiquitination of CRL substrates: associates with CRL complexes and specifically mediates addition of the first ubiquitin on CRLs targets. The initial ubiquitin is then elongated by CDC34/UBE2R1 and UBE2R2. [PMID: 25609649, PMID: 27565346, PMID: 28514442]
* **UBE2I** SUMO-conjugating enzyme UBC9; Accepts the ubiquitin-like proteins SUMO1, SUMO2, SUMO3, SUMO4 and SUMO1P1/SUMO5 from the UBLE1A-UBLE1B E1 complex and catalyzes their covalent attachment to other proteins with the help of an E3 ligase such as RANBP2, CBX4 and ZNF451. Can catalyze the formation of poly-SUMO chains. Necessary for sumoylation of FOXL2 and KAT5. Essential for nuclear architecture and chromosome segregation. Sumoylates p53/TP53 at ‘Lys-386’. Mediates sumoylation of ERCC6 which is essential for its transcription-coupled nucleotide excision repair activity. [PMID: 10788439, PMID: 11877416, PMID: 8733011]
* **ATF7** Cyclic AMP-dependent transcription factor ATF-7; Plays important functions in early cell signaling. Binds the cAMP response element (CRE) (consensus: 5’-GTGACGT[AG][AG]-3’), a sequence present in many viral and cellular promoters. Activator of the NF-ELAM1/delta-A site of the E-selectin promoter. Has no intrinsic transcriptional activity, but activates transcription on formation of JUN or FOS heterodimers. Also can bind TRE promoter sequences when heterodimerized with members of the JUN family. [PMID: 20102225, PMID: 25609649, PMID: 26496610]
* **ABL1** Tyrosine-protein kinase ABL1; Non-receptor tyrosine-protein kinase that plays a role in many key processes linked to cell growth and survival such as cytoskeleton remodeling in response to extracellular stimuli, cell motility and adhesion, receptor endocytosis, autophagy, DNA damage response and apoptosis. [PMID: 10637231, PMID: 18619508, PMID: 19818398]
* **GSK3B** Glycogen synthase kinase-3 beta; Constitutively active protein kinase that acts as a negative regulator in the hormonal control of glucose homeostasis, Wnt signaling and regulation of transcription factors and microtubules, by phosphorylating and inactivating glycogen synthase (GYS1 or GYS2), EIF2B, CTNNB1/beta-catenin, APC, AXIN1, DPYSL2/CRMP2, JUN, NFATC1/NFATC, MAPT/TAU and MACF1. Requires primed phosphorylation of the majority of its substrates. [PMID: 17215518, PMID: 1846781, PMID: 25241761]
* **HIF1A** Hypoxia-inducible factor 1-alpha; Functions as a master transcriptional regulator of the adaptive response to hypoxia. Under hypoxic conditions, activates the transcription of over 40 genes, including erythropoietin, glucose transporters, glycolytic enzymes, vascular endothelial growth factor, HILPDA, and other genes whose protein products increase oxygen delivery or facilitate metabolic adaptation to hypoxia. Plays an essential role in embryonic vascularization, tumor angiogenesis and pathophysiology of ischemic disease. [PMID: 11739718, PMID: 19738058, PMID: 25879517]
* **NR3C1** Glucocorticoid receptor; Receptor for glucocorticoids (GC). Has a dual mode of action: as a transcription factor that binds to glucocorticoid response elements (GRE), both for nuclear and mitochondrial DNA, and as a modulator of other transcription factors. Affects inflammatory responses, cellular proliferation and differentiation in target tissues. Involved in chromatin remodeling. [PMID: 14522952, PMID: 7823959, PMID: 8733011]
* **HSP90AA1** Heat shock protein HSP 90-alpha; Molecular chaperone that promotes the maturation, structural maintenance and proper regulation of specific target proteins involved for instance in cell cycle control and signal transduction. Undergoes a functional cycle that is linked to its ATPase activity which is essential for its chaperone activity. This cycle probably induces conformational changes in the client proteins, thereby causing their activation. Interacts dynamically with various co-chaperones that modulate its substrate recognition, ATPase cycle and chaperone function. [PMID: 20195357, PMID: 20936779, PMID: 25609649]
* **ESR1** Estrogen receptor; Nuclear hormone receptor. The steroid hormones and their receptors are involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Ligand-dependent nuclear transactivation involves either direct homodimer binding to a palindromic estrogen response element (ERE) sequence or association with other DNA-binding transcription factors, such as AP-1/c-Jun, c-Fos, ATF-2, Sp1 and Sp3, to mediate ERE- independent signaling. [PMID: 11477071, PMID: 17317669, PMID: 23747343]
* **BRCA1** Breast cancer type 1 susceptibility protein; E3 ubiquitin-protein ligase that specifically mediates the formation of ‘Lys-6’-linked polyubiquitin chains and plays a central role in DNA repair by facilitating cellular responses to DNA damage. It is unclear whether it also mediates the formation of other types of polyubiquitin chains. The E3 ubiquitin-protein ligase activity is required for its tumor suppressor function. [PMID: 12080089, PMID: 23339184, PMID: 25609649]
* **BATF** Basic leucine zipper transcriptional factor ATF-like; AP-1 family transcription factor that controls the differentiation of lineage-specific cells in the immune system: specifically mediates the differentiation of T-helper 17 cells (Th17), follicular T-helper cells (TfH), CD8(+) dendritic cells and class- switch recombination (CSR) in B-cells. Acts via the formation of a heterodimer with JUNB that recognizes and binds DNA sequence 5’- TGA[CG]TCA-3’. [PMID: 20102225, PMID: 23661758, PMID: 8570175]
* **TBP** TATA-box-binding protein; General transcription factor that functions at the core of the DNA-binding multiprotein factor TFIID. Binding of TFIID to the TATA box is the initial transcriptional step of the pre-initiation complex (PIC), playing a role in the activation of eukaryotic genes transcribed by RNA polymerase II. Component of a BRF2-containing transcription factor complex that regulates transcription mediated by RNA polymerase III. [PMID: 16055710, PMID: 7685215, PMID: 7848298]
* **EWSR1** RNA-binding protein EWS; Might normally function as a transcriptional repressor. EWS- fusion-proteins (EFPS) may play a role in the tumorigenic process. They may disturb gene expression by mimicking, or interfering with the normal function of CTD-POLII within the transcription initiation complex. They may also contribute to an aberrant activation of the fusion protein target genes; Belongs to the RRM TET family. [PMID: 14550555, PMID: 24999758, PMID: 25609649]
* **JDP2** Jun dimerization protein 2; Component of the AP-1 transcription factor that represses transactivation mediated by the Jun family of proteins. Involved in a variety of transcriptional responses associated with AP-1 such as UV- induced apoptosis, cell differentiation, tumorigenesis and antitumogeneris. Can also function as a repressor by recruiting histone deacetylase 3/HDAC3 to the promoter region of JUN. May control transcription via direct regulation of the modification of histones and the assembly of chromatin. [PMID: 18671972, PMID: 25609649, PMID: 9154808]
* **CREB1** Cyclic AMP-responsive element-binding protein 1; Phosphorylation-dependent transcription factor that stimulates transcription upon binding to the DNA cAMP response element (CRE), a sequence present in many viral and cellular promoters. Transcription activation is enhanced by the TORC coactivators which act independently of Ser-133 phosphorylation. Involved in different cellular processes including the synchronization of circadian rhythmicity and the differentiation of adipose cells; Belongs to the bZIP family. [PMID: 18641343, PMID: 2138276, PMID: 25609649]
* **NFATC2** Nuclear factor of activated T-cells, cytoplasmic 2; Plays a role in the inducible expression of cytokine genes in T-cells, especially in the induction of the IL-2, IL-3, IL-4, TNF-alpha or GM-CSF. Promotes invasive migration through the activation of GPC6 expression and WNT5A signaling pathway. [PMID: 20557936, PMID: 25609649, PMID: 27637333]
* **FOSB** Protein fosB; FosB interacts with Jun proteins enhancing their DNA binding activity. [[https://string-db.org/newstring\_cgi/show\_edge\_details.pl?identifiers=9606.ENSP00000360266 9606.ENSP00000245919](https://string-db.org/newstring_cgi/show_edge_details.pl?identifiers=9606.ENSP00000360266%0D9606.ENSP00000245919)]
* **JUND** Transcription factor jun-D; Transcription factor binding AP-1 sites. [[https://string-db.org/newstring\_cgi/show\_edge\_details.pl?identifiers=9606.ENSP00000360266 9606.ENSP00000252818](https://string-db.org/newstring_cgi/show_edge_details.pl?identifiers=9606.ENSP00000360266%0D9606.ENSP00000252818)]

The interactions list has been truncated to include only interactions with the strongest support from the literature.

# 5. Links to Gene Databases

* GeneCards (human): <https://www.genecards.org/cgi-bin/carddisp.pl?gene=JUN>
* Harmonizome (human): <https://maayanlab.cloud/Harmonizome/gene/JUN>
* NCBI (human): <https://www.ncbi.nlm.nih.gov/gene/3725>
* NCBI (rat): <https://www.ncbi.nlm.nih.gov/gene/24516>
* Ensemble (human): <https://useast.ensembl.org/Homo_sapiens/Gene/Summary?g=ENSG00000177606>
* Ensemble (rat): <https://useast.ensembl.org/Rattus_norvegicus/Gene/Summary?g=ENSRNOG00000026293>
* Rat Genome Database (rat): <https://rgd.mcw.edu/rgdweb/report/gene/main.html?id=2943>
* Uniprot (human): <https://www.uniprot.org/uniprotkb/P05412>
* Uniprot (rat): <https://www.uniprot.org/uniprotkb/P17325>
* Wikigenes (human): <https://www.wikigenes.org/e/gene/e/3725.html>
* Wikigenes (rat): <https://www.wikigenes.org/e/gene/e/24516.html>
* Alphafold (human): <https://alphafold.ebi.ac.uk/entry/P05412>
* Alphafold (rat): <https://alphafold.ebi.ac.uk/entry/P17325>
* PDB (human): <https://www.rcsb.org/structure/1A02>, <https://www.rcsb.org/structure/1FOS>, <https://www.rcsb.org/structure/1JNM>, <https://www.rcsb.org/structure/1JUN>, <https://www.rcsb.org/structure/1S9K>, <https://www.rcsb.org/structure/1T2K>, <https://www.rcsb.org/structure/5FV8>, <https://www.rcsb.org/structure/5T01>, <https://www.rcsb.org/structure/6Y3V>
* PDB (mouse): none
* PDB (rat): none

# 6. GO Terms, MSigDB Signatures, Pathways Containing Gene with Descriptions of Gene Sets

## **Pathways:**

**Activation of anterior HOX genes in hindbrain development during early embryogenesis:** In mammals, anterior Hox genes may be defined as paralog groups 1 to 4 (Natale et al. 2011), which are involved in development of the hindbrain through sequential expression in the rhombomeres, transient segments of the neural tube that form during development of the hindbrain (reviewed in Alexander et al. 2009, Soshnikova and Duboule 2009, Tumpel et al. 2009, Mallo et al. 2010, Andrey and Duboule 2014). Hox gene activation during mammalian development has been most thoroughly studied in mouse embryos and the results have been extended to human development by in vitro experiments with human embryonal carcinoma cells and human embryonic stem cells. Expression of a typical anterior Hox gene has an anterior boundary located at the junction between two rhombomeres and continues caudally to regulate segmentation and segmental fate in ectoderm, mesoderm, and endoderm. Anterior boundaries of expression of successive Hox paralog groups are generally separated from each other by 2 rhombomeres. For example, HOXB2 is expressed in rhombomere 3 (r3) and caudally while HOXB3 is expressed in r5 and caudally. Exceptions exist, however, as HOXA1, HOXA2, and HOXB1 do not follow the rule and HOXD1 and HOXC4 are not expressed in rhombomeres. Hox genes within a Hox cluster are expressed colinearly: the gene at the 3’ end of the cluster is expressed earliest, and hence most anteriorly, then genes 5’ are activated sequentially in the same order as they occur in the cluster [<https://reactome.org/PathwayBrowser/#/R-HSA-5617472>].

**Toll Like Receptor TLR6:TLR2 Cascade:** TLR2 and TLR4 recognize different bacterial cell wall components. While TLR4 is trained onto Gram-negative lipopolysaccharide components, TLR2 - in combination with TLR6 - plays a major role in recognizing peptidoglycan wall products from Gram-positive bacteria, as well as Mycobacterial diacylated lipopeptides. In particular, TLR6 appears to participate in discriminating the subtle differences between dipalmitoyl and tripalmitoyl cysteinyl residues (Okusawa et al. 2004) [<https://reactome.org/PathwayBrowser/#/R-HSA-168188>].

**Toll Like Receptor TLR1:TLR2 Cascade:** TLR1 is expressed by monocytes. TLR1 and TLR2 cotranslationally form heterodimeric complexes on the cell surface and in the cytosol. The TLR2:TLR1 complex recognizes Neisserial PorB and Mycobacterial triacylated lipoproteins and peptides, amongst others, triggering up-regulation of nuclear factor-kappaB production and apoptotic cascades. Such cooperation between TLR1 and TLR2 on the cell surface of normal human peripheral blood mononuclear cells, for instance, leads to the activation of pro-inflammatory cytokine secretion (Sandor et al. 2003) [<https://reactome.org/PathwayBrowser/#/R-HSA-168179>].

**Activation of the AP-1 family of transcription factors:** Activator protein-1 (AP-1) is a collective term referring to a group of transcription factors that bind to promoters of target genes in a sequence-specific manner. AP-1 family consists of hetero- and homodimers of bZIP (basic region leucine zipper) proteins, mainly of Jun-Jun, Jun-Fos or Jun-ATF. AP-1 members are involved in the regulation of a number of cellular processes including cell growth, proliferation, survival, apoptosis, differentiation, cell migration. The ability of a single transcription factor to determine a cell fate critically depends on the relative abundance of AP-1 subunits, the composition of AP-1 dimers, the quality of stimulus, the cell type, the co-factor assembly [<https://reactome.org/PathwayBrowser/#/R-HSA-450341>].

**TRIF(TICAM1)-mediated TLR4 signaling:** TRIF (TICAM1) was shown to induce IRF3/7 and NF-kappa-B activation as well as apoptosis through distinct intracellular signaling pathways (Yamamoto M et al., 2003; Fitzgerald KA et al., 2003; Han KJ et al., 2004; Kaiser WJ & Offermann MK 2005) [<https://reactome.org/PathwayBrowser/#/R-HSA-937061>].

**FCERI mediated MAPK activation:** Formation of the LAT signaling complex leads to activation of MAPK and production of cytokines. The sequence of events that leads from LAT to cytokine production has not been as clearly defined as the sequence that leads to degranulation. However, the pathways that lead to cytokine production require the guanine-nucleotide-exchange factors SOS and VAV that regulate GDP-GTP exchange of RAS. After its activation, RAS positively regulates the RAF-dependent pathway that leads to phosphorylation and, in part, activation of the mitogen-activated protein kinases (MAPKs) extracellular-signal-regulated kinase 1 (ERK1) and ERK2 (Gilfillan & Tkaczyk 2006) [<https://reactome.org/PathwayBrowser/#/R-HSA-2871796>].

**Interleukin-17 signaling:** Interleukin-17 (IL17) is a family of cytokines (Kawaguchi et al. 2004, Gu et al. 2013). IL17A, the founding member of the family is able to induce the production of other cytokines and chemokines, such as IL6, IL8, and granulocyte colony-stimulating factor (G-CSF) in a variety of cell types, including activated T-cells. It plays a pivotal role in host defenses in response to microbial infection and is involved in the pathogenesis of autoimmune diseases and allergic syndromes. IL17 activates several downstream signaling pathways including NFkB, MAPKs and C/EBPs, inducing the expression of antibacterial peptides, proinflammatory chemokines and cytokines and matrix metalloproteases (MMPs). IL17 can stabilize the mRNA of genes induced by TNF-alpha. IL17 signal transduction is mediated by the cytosolic adaptor molecule ACT1 (also known as CIKS) [<https://reactome.org/PathwayBrowser/#/R-HSA-448424>].

**MyD88 cascade initiated on plasma membrane:** Mammalian myeloid differentiation factor 88 (MyD88) is Toll/interleukin (IL)-1 (TIR)-domain containing adapter protein which plays crucial role in TLR signaling. All TLRs, with only one exception of TLR3, can initiate downstream signaling through MyD88. In the MyD88 - dependent pathway, once the adaptor is bound to TLR it leads to recruitment of IL1 receptor associated kinase family IRAK which is followed by activation of tumour necrosis factor receptor-associated factor 6 (TRAF6) . TRAF6 is an ubiquitin E3 ligase which in turn induces TGF-beta activating kinase 1 (TAK1) auto phosphorylation. Once activated TAK1 can ultimately mediate the induction of the transcription factor NF-kB or the mitogen-activated protein kinases (MAPK), such as JNK, p38 and ERK. This results in the translocation of the activated NF-kB and MAPKs to the nucleus and the initiation of appropriate gene transcription leading to the production of many proinflammatory cytokines and antimicrobial peptides [<https://reactome.org/PathwayBrowser/#/R-HSA-975871>].

**TRAF6 mediated induction of NFkB and MAP kinases upon TLR7/8 or 9 activation:** TRAF6 mediates NFkB activation via canonical phosphorylation of IKK complex by TAK1. TRAF6 and TAK1 also regulate MAPK cascades leading to the activation of AP-1 [<https://reactome.org/PathwayBrowser/#/R-HSA-975138>].

**MyD88:MAL(TIRAP) cascade initiated on plasma membrane:** The first known downstream component of TLR4 and TLR2 signaling is the adaptor MyD88. Another adapter MyD88-adaptor-like (Mal; also known as TIR-domain-containing adaptor protein or TIRAP) has also been described for TLR4 and TLR2 signaling. MyD88 comprises an N-terminal Death Domain (DD) and a C-terminal TIR, whereas Mal lacks the DD. The TIR homotypic interactions bring adapters into contact with the activated TLRs, whereas the DD modules recruit serine/threonine kinases such as interleukin-1-receptor-associated kinase (IRAK). Recruitment of these protein kinases is accompanied by phosphorylation, which in turn results in the interaction of IRAKs with TNF-receptor-associated factor 6 (TRAF6). The oligomerization of TRAF6 activates TAK1, a member of the MAP3-kinase family, and this leads to the activation of the IkB kinases. These kinases, in turn, phosphorylate IkB, leading to its proteolytic degradation and the translocation of NF-kB to the nucleus. Concomitantly, members of the activator protein-1 (AP-1) transcription factor family, Jun and Fos, are activated, and both AP-1 transcription factors and NF-kB are required for cytokine production, which in turn produces downstream inflammatory effects [<https://reactome.org/PathwayBrowser/#/R-HSA-166058>].

**MyD88-independent TLR4 cascade:** The MyD88-independent signaling pathway is shared by TLR3 and TLR4 cascades. TIR-domain-containing adapter-inducing interferon-beta (TRIF or TICAM1) is a key adapter molecule in transducing signals from TLR3 and TLR4 in a MyD88-independent manner (Yamamoto M et al. 2003a). TRIF is recruited to the ligand-stimulated TLR3 or 4 complex via its TIR domain. TLR3 directly binds TRIF (Oshiumi H et al 2003). In contrast, the TLR4-mediated signaling pathway requires two adapter molecules, TRAM (TRIF-related adapter molecule or TICAM2) and TRIF. TRAM(TICAM2) is thought to bridge the activated TLR4 complex and TRIF (Yamamoto M et al. 2003b, Tanimura N et al. 2008, Kagan JC et al. 2008) [<https://reactome.org/PathwayBrowser/#/R-HSA-166166>].

**Toll Like Receptor 10 (TLR10) Cascade:** Little is known about TLR10 ligands. It has been established that the receptor homodimerizes upon binding and signals in an MyD88-dependent manner (Hasan U et al 2005; Nyman T et al 2008). It may also heterodimerize with TLRs 1 and 2. It is expressed in a restricted fashion as a highly N-glycosylated protein detectable in B cells and dendritic cells [<https://reactome.org/PathwayBrowser/#/R-HSA-168142>].

**Toll Like Receptor 7/8 (TLR7/8) Cascade:** RNA can serve as a danger signal, both in its double-stranded form as well as single-stranded RNA (ssRNA). Toll like receptor 7 (TLR7) and TLR8 are endosomal receptors that sense ssRNA oligonucleotides containing guanosine (G)- and uridine (U)-rich sequences from RNA viruses (Jurk M et al. 2002; Heil F et al. 2004; Diebold SS et al. 2004; Li Y et al. 2013; reviewed in Lester SN & Li K 2014). TLR7 is primarily expressed in plasmacytoid dendritic cells (pDCs) and, to some extent, in B cells, monocytes and macrophages, whereas TLR8 is mostly expressed in monocytes, macrophages and myeloid DCs. Upon engagement of ssRNAs in endosomes, TLR7/8 initiate the myeloid differentiation factor 88 (MyD88)-dependent pathway, culminating in synthesis of type I and type III IFNs and proinflammatory mediators via activation of IFN regulatory factor 7 (IRF7) and NF-?B, respectively, depending on the cell type (reviewed in Lester SN & Li K 2014) [<https://reactome.org/PathwayBrowser/#/R-HSA-168181>].

**Estrogen-dependent gene expression:** Estrogens mediate their transcriptional effects through interaction with the estrogen receptors, ESR1 (also known as ER alpha) and ESR2 (ER beta). ESR1 and ESR2 share overlapping but distinct functions, with ESR1 playing the primary role in transcriptional activation in most cell types (Hah and Krauss, 2014; Haldosen et al, 2014. The receptors function as ligand-dependent dimers and can activate target genes either through direct binding to an estrogen responsive element (ERE) in the target gene promoter, or indirectly through interaction with another DNA-binding protein such as RUNX1, SP1, AP1 or NF-kappa beta (reviewed in Bai and Gust, 2009; Hah and Krause, 2014). Binding of estrogen receptors to the DNA promotes the assembly of higher order transcriptional complexes containing methyltransferases, histone acetyltransferases and other transcriptional activators, which promote transcription by establishing active chromatin marks and by recruiting general transcription factors and RNA polymerase II. ESR1- and estrogen-dependent recruitment of up to hundreds of coregulators has been demonstrated by varied co-immunoprecipitation and proteomic approaches (Kittler et al, 2013; Mohammed et al, 2013; Foulds et al, 2013; Mohammed et al, 2015; Liu et al, 2014; reviewed in Magnani and Lupien, 2014; Arnal, 2017). In some circumstances, ligand-bound receptors can also promote the assembly of a repression complex at a target gene, and in some cases, heterodimers of ESR1 and ESR2 serve as repressors of ESR1-mediated target gene activation (reviewed in Hah and Kraus, 2014; Arnal et al, 2017). Phosphorylation of the estrogen receptor also modulates its activity, and provides cross-talk between nuclear estrogen-dependent signaling and non-genomic estrogen signaling from the plasma membrane (reviewed in Anbalagan and Rowan, 2015; Haldosen et al, 2014; Schwartz et al, 2016) [<https://reactome.org/PathwayBrowser/#/R-HSA-9018519>].

**MAPK6/MAPK4 signaling:** MAPK6 and MAPK4 (also known as ERK3 and ERK4) are vertebrate-specific atypical MAP kinases. Atypical MAPK are less well characterized than their conventional counterparts, and are generally classified as such based on their lack of activation by MAPKK family members. Unlike the conventional MAPK proteins, which contain a Thr-X-Tyr motif in the activation loop, MAPK6 and 4 have a single Ser-Glu-Gly phospho-acceptor motif (reviewed in Coulombe and Meloche, 2007; Cargnello et al, 2011). MAPK6 is also distinct in being an unstable kinase, whose turnover is mediated by ubiquitin-dependent degradation (Coulombe et al, 2003; Coulombe et al, 2004). The biological functions and pathways governing MAPK6 and 4 are not well established. MAPK6 and 4 are phosphorylated downstream of class I p21 activated kinases (PAKs) in a RAC- or CDC42-dependent manner (Deleris et al, 2008; Perander et al, 2008; Deleris et al, 2011; De La Mota-Peynado et al, 2011). One of the only well established substrates of MAPK6 and 4 is MAPKAPK5, which contributes to cell motility by promoting the HSBP1-dependent rearrangement of F-actin (Gerits et al, 2007; Kostenko et al, 2009a; reviewed in Kostenko et al, 2011b). The atypical MAPKs also contribute to cell motility and invasiveness through the NCOA3:ETV4-dependent regulation of MMP gene expression (Long et al, 2012; Yan et al, 2008; Qin et al, 2008). Both of these pathways may be misregulated in human cancers (reviewed in Myant and Sansom, 2011; Kostenko et al, 2012) [<https://reactome.org/PathwayBrowser/#/R-HSA-5687128>].

**PIP3 activates AKT signaling:** Signaling by AKT is one of the key outcomes of receptor tyrosine kinase (RTK) activation. AKT is activated by the cellular second messenger PIP3, a phospholipid that is generated by PI3K. In ustimulated cells, PI3K class IA enzymes reside in the cytosol as inactive heterodimers composed of p85 regulatory subunit and p110 catalytic subunit. In this complex, p85 stabilizes p110 while inhibiting its catalytic activity. Upon binding of extracellular ligands to RTKs, receptors dimerize and undergo autophosphorylation. The regulatory subunit of PI3K, p85, is recruited to phosphorylated cytosolic RTK domains either directly or indirectly, through adaptor proteins, leading to a conformational change in the PI3K IA heterodimer that relieves inhibition of the p110 catalytic subunit. Activated PI3K IA phosphorylates PIP2, converting it to PIP3; this reaction is negatively regulated by PTEN phosphatase. PIP3 recruits AKT to the plasma membrane, allowing TORC2 to phosphorylate a conserved serine residue of AKT. Phosphorylation of this serine induces a conformation change in AKT, exposing a conserved threonine residue that is then phosphorylated by PDPK1 (PDK1). Phosphorylation of both the threonine and the serine residue is required to fully activate AKT. The active AKT then dissociates from PIP3 and phosphorylates a number of cytosolic and nuclear proteins that play important roles in cell survival and metabolism. For a recent review of AKT signaling, please refer to Manning and Cantley, 2007 [<https://reactome.org/PathwayBrowser/#/R-HSA-1257604>].

**Pre-NOTCH Transcription and Translation:** In humans, the NOTCH protein family has four members: NOTCH1, NOTCH2, NOTCH3 and NOTCH4. NOTCH1 protein was identified first, as the product of a chromosome 9 gene translocated in T-cell acute lymphoblastic leukemia that was homologous to Drosophila Notch (Ellisen et al. 1991). At the same time, rat Notch1 was cloned (Weinmaster et al. 1991), followed by cloning of mouse Notch1, named Motch (Del Amo et al. 1992). NOTCH2 protein is the product of a gene on chromosome 1 (Larsson et al. 1994). NOTCH2 expression is differentially regulated during B-cell development (Bertrand et al. 2000). NOTCH2 mutations are a rare cause of Alagille syndrome (McDaniell et al. 2006). NOTCH3 is the product of a gene on chromosome 19. NOTCH3 mutations are the underlying cause of CADASIL, cerebral arteriopathy with subcortical infarcts and leukoencephalopathy (Joutel et al. 1996). NOTCH4, the last NOTCH protein discovered, is the product of a gene on chromosome 6 (Li et al. 1998) [<https://reactome.org/PathwayBrowser/#/R-HSA-1912408>].

**Regulation of PTEN gene transcription:** Transcription of the PTEN gene is regulated at multiple levels. Epigenetic repression involves the recruitment of Mi-2/NuRD upon SALL4 binding to the PTEN promoter (Yang et al. 2008, Lu et al. 2009) or EVI1-mediated recruitment of the polycomb repressor complex (PRC) to the PTEN promoter (Song et al. 2009, Yoshimi et al. 2011). Transcriptional regulation is also elicited by negative regulators, including NR2E1:ATN1 (atrophin-1) complex, JUN (c-Jun), SNAIL and SLUG (Zhang et al. 2006, Vasudevan et al. 2007, Escriva et al. 2008, Uygur et al. 2015) and positive regulators such as TP53 (p53), MAF1, ATF2, EGR1 or PPARG (Stambolic et al. 2001, Virolle et al. 2001, Patel et al. 2001, Shen et al. 2006, Li et al. 2016) [<https://reactome.org/PathwayBrowser/#/R-HSA-8943724>].

**Senescence-Associated Secretory Phenotype (SASP):** The culture medium of senescent cells in enriched in secreted proteins when compared with the culture medium of quiescent i.e. presenescent cells and these secreted proteins constitute the so-called senescence-associated secretory phenotype (SASP), also known as the senescence messaging secretome (SMS). SASP components include inflammatory and immune-modulatory cytokines (e.g. IL6 and IL8), growth factors (e.g. IGFBPs), shed cell surface molecules (e.g. TNF receptors) and survival factors. While the SASP exhibits a wide ranging profile, it is not significantly affected by the type of senescence trigger (oncogenic signalling, oxidative stress or DNA damage) or the cell type (epithelial vs. mesenchymal) (Coppe et al. 2008). However, as both oxidative stress and oncogenic signaling induce DNA damage, the persistent DNA damage may be a deciding SASP initiator (Rodier et al. 2009). SASP components function in an autocrine manner, reinforcing the senescent phenotype (Kuilman et al. 2008, Acosta et al. 2008), and in the paracrine manner, where they may promote epithelial-to-mesenchymal transition (EMT) and malignancy in the nearby premalignant or malignant cells (Coppe et al. 2008). Interleukin-1-alpha (IL1-alpha), a minor SASP component whose transcription is stimulated by the AP-1 (FOS:JUN) complex (Bailly et al. 1996), can cause paracrine senescence through IL1 and inflammasome signaling (Acosta et al. 2013) [<https://reactome.org/PathwayBrowser/#/R-HSA-2559582>].

**Oxidative Stress Induced Senescence:** Oxidative stress, caused by increased concentration of reactive oxygen species (ROS) in the cell, can happen as a consequence of mitochondrial dysfunction induced by the oncogenic RAS (Moiseeva et al. 2009) or independent of oncogenic signaling. Prolonged exposure to interferon-beta (IFNB, IFN-beta) also results in ROS increase (Moiseeva et al. 2006). ROS oxidize thioredoxin (TXN), which causes TXN to dissociate from the N-terminus of MAP3K5 (ASK1), enabling MAP3K5 to become catalytically active (Saitoh et al. 1998). ROS also stimulate expression of Ste20 family kinases MINK1 (MINK) and TNIK through an unknown mechanism, and MINK1 and TNIK positively regulate MAP3K5 activation (Nicke et al. 2005) [<https://reactome.org/PathwayBrowser/#/R-HSA-2559580>].

**TP53 Regulates Transcription of DNA Repair Genes:** Several DNA repair genes contain p53 response elements and their transcription is positively regulated by TP53 (p53). TP53-mediated regulation probably ensures increased protein level of DNA repair genes under genotoxic stress [<https://reactome.org/PathwayBrowser/#/R-HSA-6796648>].

**Deregulated CDK5 triggers multiple neurodegenerative pathways in Alzheimer’s disease models:** Post-mitotic neurons do not have an active cell cycle. However, deregulation of Cyclin Dependent Kinase-5 (CDK5) activity in these neurons can aberrantly activate various components of cell cycle leading to neuronal death (Chang et al. 2012). Random activation of cell cycle proteins has been shown to play a key role in the pathogenesis of several neurodegenerative disorders (Yang et al. 2003, Lopes et al. 2009). CDK5 is not activated by the canonical cyclins, but binds to its own specific partners, CDK5R1 and CDK5R2 (aka p35 and p39, respectively) (Tsai et al. 1994, Tang et al. 1995). Expression of p35 is nearly ubiquitous, whereas p39 is largely expressed in the central nervous system. A variety of neurotoxic insults such as beta-amyloid (A-beta), ischemia, excitotoxicity and oxidative stress disrupt the intracellular calcium homeostasis in neurons, thereby leading to the activation of calpain, which cleaves p35 into p25 and p10 (Lee et al. 2000). p25 has a six-fold longer half-life compared to p35 and lacks the membrane anchoring signal, which results in its constitutive activation and mislocalization of the CDK5:p25 complex to the cytoplasm and the nucleus. There, CDK5:p25 is able to access and phosphorylate a variety of atypical targets, triggering a cascade of neurotoxic pathways that culminate in neuronal death. One such neurotoxic pathway involves CDK5-mediated random activation of cell cycle proteins which culminate in neuronal death. Exposure of primary cortical neurons to oligomeric beta-amyloid (1-42) hyper-activates CDK5 due to p25 formation, which in turn phosphorylates CDC25A, CDC25B and CDC25C. CDK5 phosphorylates CDC25A at S40, S116 and S261; CDC25B at S50, T69, S160, S321 and S470; and CDC25C at T48, T67, S122, T130, S168 and S214. CDK5-mediated phosphorylation of CDC25A, CDC25B and CDC25C not only increases their phosphatase activities but also facilitates their release from 14-3-3 inhibitory binding. CDC25A, CDC25B and CDC25C in turn activate CDK1, CDK2 and CDK4 kinases causing neuronal death. Consistent with this mechanism, higher CDC25A, CDC25B and CDC25C activities were observed in human Alzheimer’s disease (AD) clinical samples, as compared to age-matched controls. Inhibition of CDC25 isoforms confers neuroprotection to beta-amyloid toxicity, which underscores the contribution of this pathway to AD pathogenesis [<https://reactome.org/PathwayBrowser/#/R-HSA-8862803>].

**WNT5:FZD7-mediated leishmania damping:** Wnt-5a (WNT5) is known for being a highly specific regulated gene in response to microbial infection (Blumenthal et al. 2006, Pereira et al. 2008 & Ljungberg et al. 2019) including leishmaniasis (Chakraborty et al. 2017), where it seems to be involve in mechanisms that dampen the parasite load within main host macrophages (Chakraborty et al. 2017). In addition, WNT5 is a highly responsive gene in human macrophages present in chronic diseases such as rheumatoid arthritis (Sen et al. 2000), cancer (Pukrop et al. 2006), atherosclerosis (Christman et al. 2008) and obesity (Ouchi et al. 2010 & Ljungberg et al. 2019) [<https://reactome.org/PathwayBrowser/#/R-HSA-9673324>].

**Activation of anterior HOX genes in hindbrain development during early embryogenesis:** In mammals, anterior Hox genes may be defined as paralog groups 1 to 4 (Natale et al. 2011), which are involved in development of the hindbrain through sequential expression in the rhombomeres, transient segments of the neural tube that form during development of the hindbrain (reviewed in Alexander et al. 2009, Soshnikova and Duboule 2009, Tumpel et al. 2009, Mallo et al. 2010, Andrey and Duboule 2014). Hox gene activation during mammalian development has been most thoroughly studied in mouse embryos and the results have been extended to human development by in vitro experiments with human embryonal carcinoma cells and human embryonic stem cells [<https://reactome.org/PathwayBrowser/#/R-HSA-5617472>].

## GO terms:

**DNA-templated transcription** [The synthesis of an RNA transcript from a DNA template. GO:0006351]

**SMAD protein signal transduction** [An intracellular signal transduction pathway that starts with the activation of a SMAD protein, leading to the formation of a complex with co-SMADs, which translocates to the nucleus, where it regulates transcription of specific target genes.|Note that the upstream receptor and its ligand regulate the pathway (and are not part of the SMAD pathway), since it is an intracellular signaling pathway. GO:0060395]

**angiogenesis** [Blood vessel formation when new vessels emerge from the proliferation of pre-existing blood vessels. GO:0001525]

**apoptotic process** [A programmed cell death process which begins when a cell receives an internal (e.g. DNA damage) or external signal (e.g. an extracellular death ligand), and proceeds through a series of biochemical events (signaling pathway phase) which trigger an execution phase. The execution phase is the last step of an apoptotic process, and is typically characterized by rounding-up of the cell, retraction of pseudopodes, reduction of cellular volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), plasma membrane blebbing and fragmentation of the cell into apoptotic bodies. When the execution phase is completed, the cell has died. GO:0006915]

**axon regeneration** [The regrowth of axons following their loss or damage. GO:0031103]

**cell population proliferation** [The multiplication or reproduction of cells, resulting in the expansion of a cell population.|This term was moved out from being a child of ‘cellular process’ because it is a cell population-level process, and cellular processes are restricted to those processes that involve individual cells. Also note that this term is intended to be used for the proliferation of cells within a multicellular organism, not for the expansion of a population of single-celled organisms. GO:0008283]

**cellular response to anisomycin** [Any process that results in a change in state or activity of a cell (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of an anisomycin stimulus. GO:0072740]

**cellular response to cadmium ion** [Any process that results in a change in state or activity of a cell (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a cadmium (Cd) ion stimulus. GO:0071276]

**cellular response to calcium ion** [Any process that results in a change in state or activity of a cell (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a calcium ion stimulus. GO:0071277]

**cellular response to hypoxia** [Any process that results in a change in state or activity of a cell (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a stimulus indicating lowered oxygen tension. Hypoxia, defined as a decline in O2 levels below normoxic levels of 20.8 - 20.95%, results in metabolic adaptation at both the cellular and organismal level.|Note that this term should not be confused with ‘cellular response to anoxia ; GO:0071454’. Note that in laboratory studies, hypoxia is typically studied at O2 concentrations ranging from 0.1 - 5%. GO:0071456]

**cellular response to lipopolysaccharide** [Any process that results in a change in state or activity of a cell (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a lipopolysaccharide stimulus; lipopolysaccharide is a major component of the cell wall of gram-negative bacteria. GO:0071222]

**cellular response to potassium ion starvation** [Any process that results in a change in state or activity of a cell (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of deprivation of potassium ions. GO:0051365]

**cellular response to prolactin** [Any process that results in a change in state or activity of a cell (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a prolactin stimulus. GO:1990646]

**cellular response to reactive oxygen species** [Any process that results in a change in state or activity of a cell (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a reactive oxygen species stimulus. Reactive oxygen species include singlet oxygen, superoxide, and oxygen free radicals. GO:0034614]

**cellular response to zinc ion starvation** [Any process that results in a change in state or activity of a cell (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of deprivation of zinc ions. GO:0034224]

**circadian rhythm** [Any biological process in an organism that recurs with a regularity of approximately 24 hours. GO:0007623]

**eyelid development in camera-type eye** [The progression of the eyelid in a camera-type eye from its formation to the mature state. The eyelid is a membranous cover that helps protect and lubricate the eye. GO:0061029]

**immune response** [Any immune system process that functions in the calibrated response of an organism to a potential internal or invasive threat. GO:0006955]

**leading edge cell differentiation** [The process in which relatively unspecialized cells acquire specialized structural and/or functional features of leading edge cells, cells at the front of a migrating epithelial sheet. GO:0035026]

**learning** [Any process in an organism in which a relatively long-lasting adaptive behavioral change occurs as the result of experience. GO:0007612]

**liver development** [The process whose specific outcome is the progression of the liver over time, from its formation to the mature structure. The liver is an exocrine gland which secretes bile and functions in metabolism of protein and carbohydrate and fat, synthesizes substances involved in the clotting of the blood, synthesizes vitamin A, detoxifies poisonous substances, stores glycogen, and breaks down worn-out erythrocytes. GO:0001889]

**membrane depolarization** [The process in which membrane potential decreases with respect to its steady-state potential, usually from negative potential to a more positive potential. For example, the initial depolarization during the rising phase of an action potential is in the direction from the negative steady-state resting potential towards the positive membrane potential that will be the peak of the action potential. GO:0051899]

**microglial cell activation** [The change in morphology and behavior of a microglial cell resulting from exposure to a cytokine, chemokine, cellular ligand, or soluble factor. GO:0001774]

**monocyte differentiation** [The process in which a relatively unspecialized myeloid precursor cell acquires the specialized features of a monocyte. GO:0030224]

**negative regulation of DNA-templated transcription** [Any process that stops, prevents, or reduces the frequency, rate or extent of cellular DNA-templated transcription. GO:0045892]

**negative regulation of apoptotic process** [Any process that stops, prevents, or reduces the frequency, rate or extent of cell death by apoptotic process.|This term should only be used when it is not possible to determine which phase or subtype of the apoptotic process is negatively regulated by a gene product. Whenever detailed information is available, the more granular children terms should be used. GO:0043066]

**negative regulation of cell population proliferation** [Any process that stops, prevents or reduces the rate or extent of cell proliferation. GO:0008285]

**negative regulation of neuron apoptotic process** [Any process that stops, prevents, or reduces the frequency, rate or extent of cell death by apoptotic process in neurons. GO:0043524]

**negative regulation of protein autophosphorylation** [Any process that stops, prevents or decreases the rate of the phosphorylation by a protein of one or more of its own residues. GO:0031953]

**negative regulation of transcription by RNA polymerase II** [Any process that stops, prevents, or reduces the frequency, rate or extent of transcription mediated by RNA polymerase II. GO:0000122]

**obsolete negative regulation of transcription from RNA polymerase II promoter in response to endoplasmic reticulum stress** [Any process that stops, prevents, or reduces the frequency, rate or extent of transcription from an RNA polymerase II promoter as a result of an endoplasmic reticulum stress. GO:1990441]

**outflow tract morphogenesis** [The process in which the anatomical structures of the outflow tract are generated and organized. The outflow tract is the portion of the heart through which blood flows into the arteries. GO:0003151]

**positive regulation of DNA replication** [Any process that activates or increases the frequency, rate or extent of DNA replication. GO:0045740]

**positive regulation of DNA-templated transcription** [Any process that activates or increases the frequency, rate or extent of cellular DNA-templated transcription. GO:0045893]

**positive regulation of DNA-templated transcription initiation** [Any process that activates or increases the frequency, rate or extent of DNA-templated transcription initiation. GO:2000144]

**positive regulation of ERK1 and ERK2 cascade** [Any process that activates or increases the frequency, rate or extent of signal transduction mediated by the ERK1 and ERK2 cascade. GO:0070374]

**positive regulation of apoptotic process** [Any process that activates or increases the frequency, rate or extent of cell death by apoptotic process.|This term should only be used when it is not possible to determine which phase or subtype of the apoptotic process is positively regulated by a gene product. Whenever detailed information is available, the more granular children terms should be used. GO:0043065]

**positive regulation of cell population proliferation** [Any process that activates or increases the rate or extent of cell proliferation. GO:0008284]

**positive regulation of endothelial cell proliferation** [Any process that activates or increases the rate or extent of endothelial cell proliferation. GO:0001938]

**positive regulation of epithelial cell migration** [Any process that activates or increases the frequency, rate or extent of epithelial cell migration. GO:0010634]

**positive regulation of fibroblast proliferation** [Any process that activates or increases the frequency, rate or extent of multiplication or reproduction of fibroblast cells. GO:0048146]

**positive regulation of miRNA transcription** [Any process that activates or increases the frequency, rate or extent of microRNA (miRNA) gene transcription. GO:1902895]

**positive regulation of monocyte differentiation** [Any process that activates or increases the frequency, rate or extent of monocyte differentiation. GO:0045657]

**positive regulation of neuron apoptotic process** [Any process that activates or increases the frequency, rate or extent of cell death of neurons by apoptotic process. GO:0043525]

**positive regulation of smooth muscle cell proliferation** [Any process that activates or increases the rate or extent of smooth muscle cell proliferation. GO:0048661]

**positive regulation of transcription by RNA polymerase II** [Any process that activates or increases the frequency, rate or extent of transcription from an RNA polymerase II promoter. GO:0045944]

**positive regulation of vascular associated smooth muscle cell proliferation** [Any process that activates or increases the frequency, rate or extent of vascular smooth muscle cell proliferation. GO:1904707]

**regulation of DNA-templated transcription** [Any process that modulates the frequency, rate or extent of cellular DNA-templated transcription. GO:0006355]

**regulation of cell cycle** [Any process that modulates the rate or extent of progression through the cell cycle. GO:0051726]

**regulation of cell population proliferation** [Any process that modulates the frequency, rate or extent of cell proliferation. GO:0042127]

**regulation of transcription by RNA polymerase II** [Any process that modulates the frequency, rate or extent of transcription mediated by RNA polymerase II. GO:0006357]

**release from viral latency** [The process by which a virus begins to replicate following a latency replication decision (switch). GO:0019046]

**release of cytochrome c from mitochondria** [The process that results in the movement of cytochrome c from the mitochondrial intermembrane space into the cytosol, which is part of the apoptotic signaling pathway and leads to caspase activation.|The release of cytochrome c from mitochondria is a central event in the signaling phase of the apoptotic process, and it is often used by researchers to monitor this type of cell death. Any event that induces apoptosis will at some point induce the release of cytochrome c from mitochondria. Therefore, this term should only be used to annotate gene products that are directly involved in this process. An example is Drp1 (DNM1L, UniProt symbol O00429) in PMID: 20850011. GO:0001836]

**response to cAMP** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a cAMP (cyclic AMP, adenosine 3’,5’-cyclophosphate) stimulus. GO:0051591]

**response to cytokine** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a cytokine stimulus. GO:0034097]

**response to ethanol** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of an ethanol stimulus. GO:0045471]

**response to hydrogen peroxide** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a hydrogen peroxide (H2O2) stimulus. GO:0042542]

**response to insulin** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of an insulin stimulus. Insulin is a polypeptide hormone produced by the islets of Langerhans of the pancreas in mammals, and by the homologous organs of other organisms. GO:0032868]

**response to lipopolysaccharide** [Any process that results in a change in state or activity of an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a lipopolysaccharide stimulus; lipopolysaccharide is a major component of the cell wall of gram-negative bacteria. GO:0032496]

**response to mechanical stimulus** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a mechanical stimulus. GO:0009612]

**response to muscle stretch** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a myofibril being extended beyond its slack length. GO:0035994]

**response to organic cyclic compound** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of an organic cyclic compound stimulus. GO:0014070]

**response to organic substance** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of an organic substance stimulus. GO:0010033]

**response to steroid hormone** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a steroid hormone stimulus. GO:0048545]

**response to xenobiotic stimulus** [Any process that results in a change in state or activity of a cell or an organism (in terms of movement, secretion, enzyme production, gene expression, etc.) as a result of a stimulus from a xenobiotic, a compound foreign to the organism exposed to it. It may be synthesized by another organism (like ampicillin) or it can be a synthetic chemical. GO:0009410]

**transcription by RNA polymerase II** [The synthesis of RNA from a DNA template by RNA polymerase II (RNAP II), originating at an RNA polymerase II promoter. Includes transcription of messenger RNA (mRNA) and certain small nuclear RNAs (snRNAs). GO:0006366]

**transforming growth factor beta receptor signaling pathway** [The series of molecular signals initiated by an extracellular ligand binding to a transforming growth factor beta receptor on the surface of a target cell, and ending with the regulation of a downstream cellular process, e.g. transcription. GO:0007179]

## MSigDB Signatures:

**BIOCARTA\_KERATINOCYTE\_PATHWAY**: Keratinocyte Differentiation [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_KERATINOCYTE\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_KERATINOCYTE_PATHWAY.html)

**DAZARD\_RESPONSE\_TO\_UV\_NHEK\_UP**: Genes up-regulated in NHEK cells (normal keratinocytes) by UV-B irradiation. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/DAZARD\_RESPONSE\_TO\_UV\_NHEK\_UP.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/DAZARD_RESPONSE_TO_UV_NHEK_UP.html)

**WP\_HAIR\_FOLLICLE\_DEVELOPMENT\_CYTODIFFERENTIATION\_PART\_3\_OF\_3**: Hair follicle development cytodifferentiation part 3 of 3 [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_HAIR\_FOLLICLE\_DEVELOPMENT\_CYTODIFFERENTIATION\_PART\_3\_OF\_3.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_HAIR_FOLLICLE_DEVELOPMENT_CYTODIFFERENTIATION_PART_3_OF_3.html)

**CHASSOT\_SKIN\_WOUND**: List of the transcription factors up-regulated 1 hr after wounding HDF cells (dermal fibroblasts). [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/CHASSOT\_SKIN\_WOUND.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/CHASSOT_SKIN_WOUND.html)

**HAMAI\_APOPTOSIS\_VIA\_TRAIL\_DN**: Genes down-regulated in T1 cells (primary melanoma, sensitive to TRAIL [GeneID=8743]) compared to G1 cells (metastatic melanoma, resistant to TRAIL). [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/HAMAI\_APOPTOSIS\_VIA\_TRAIL\_DN.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/HAMAI_APOPTOSIS_VIA_TRAIL_DN.html)

**REACTOME\_CELLULAR\_RESPONSES\_TO\_STIMULI**: Cellular responses to stimuli [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_CELLULAR\_RESPONSES\_TO\_STIMULI.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_CELLULAR_RESPONSES_TO_STIMULI.html)

**REACTOME\_INNATE\_IMMUNE\_SYSTEM**: Innate Immune System [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_INNATE\_IMMUNE\_SYSTEM.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_INNATE_IMMUNE_SYSTEM.html)

**WP\_WNT\_SIGNALING**: Wnt signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_WNT\_SIGNALING.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_WNT_SIGNALING.html)

**WP\_AGE\_RAGE\_PATHWAY**: AGE RAGE pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_AGE\_RAGE\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_AGE_RAGE_PATHWAY.html)

**MARTENS\_TRETINOIN\_RESPONSE\_DN**: Genes down-regulated in NB4 cells (acute promyelocytic leukemia, APL) in response to tretinoin [PubChem=444795]; based on Chip-seq data. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/MARTENS\_TRETINOIN\_RESPONSE\_DN.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/MARTENS_TRETINOIN_RESPONSE_DN.html)

**REACTOME\_CELLULAR\_SENESCENCE**: Cellular Senescence [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_CELLULAR\_SENESCENCE.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_CELLULAR_SENESCENCE.html)

**REACTOME\_SENESCENCE\_ASSOCIATED\_SECRETORY\_PHENOTYPE\_SASP**: Senescence-Associated Secretory Phenotype (SASP) [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_SENESCENCE\_ASSOCIATED\_SECRETORY\_PHENOTYPE\_SASP.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_SENESCENCE_ASSOCIATED_SECRETORY_PHENOTYPE_SASP.html)

**GENTILE\_UV\_RESPONSE\_CLUSTER\_D8**: Cluster d8: genes progressively down-regulated in WS1 cells (fibroblast) through 18 h after irradiation with high dose UV-C. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/GENTILE\_UV\_RESPONSE\_CLUSTER\_D8.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/GENTILE_UV_RESPONSE_CLUSTER_D8.html)

**KEGG\_WNT\_SIGNALING\_PATHWAY**: Wnt signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG\_WNT\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG_WNT_SIGNALING_PATHWAY.html)

**PETROVA\_ENDOTHELIUM\_LYMPHATIC\_VS\_BLOOD\_DN**: Genes down-regulated in BEC (blood endothelial cells) compared to LEC (lymphatic endothelial cells). [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PETROVA\_ENDOTHELIUM\_LYMPHATIC\_VS\_BLOOD\_DN.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PETROVA_ENDOTHELIUM_LYMPHATIC_VS_BLOOD_DN.html)

**KEGG\_FOCAL\_ADHESION**: Focal adhesion [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG\_FOCAL\_ADHESION.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG_FOCAL_ADHESION.html)

**WP\_FOCAL\_ADHESION**: Focal adhesion [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_FOCAL\_ADHESION.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_FOCAL_ADHESION.html)

**REACTOME\_INFECTIOUS\_DISEASE**: Infectious disease [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_INFECTIOUS\_DISEASE.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_INFECTIOUS_DISEASE.html)

**WP\_TH17\_CELL\_DIFFERENTIATION\_PATHWAY**: Th17 cell differentiation pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_TH17\_CELL\_DIFFERENTIATION\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_TH17_CELL_DIFFERENTIATION_PATHWAY.html)

**WP\_INSULIN\_SIGNALING**: Insulin signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_INSULIN\_SIGNALING.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_INSULIN_SIGNALING.html)

**REACTOME\_SIGNALING\_BY\_NUCLEAR\_RECEPTORS**: Signaling by Nuclear Receptors [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_SIGNALING\_BY\_NUCLEAR\_RECEPTORS.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_SIGNALING_BY_NUCLEAR_RECEPTORS.html)

**WP\_TGF\_BETA\_RECEPTOR\_SIGNALING**: TGF beta receptor signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_TGF\_BETA\_RECEPTOR\_SIGNALING.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_TGF_BETA_RECEPTOR_SIGNALING.html)

**KOKKINAKIS\_METHIONINE\_DEPRIVATION\_48HR\_UP**: Genes up-regulated in MEWO cells (melanoma) after 48h of methionine [PubChem=876] deprivation. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KOKKINAKIS\_METHIONINE\_DEPRIVATION\_48HR\_UP.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KOKKINAKIS_METHIONINE_DEPRIVATION_48HR_UP.html)

**BIOCARTA\_INTEGRIN\_PATHWAY**: Integrin Signaling Pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_INTEGRIN\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_INTEGRIN_PATHWAY.html)

**PID\_ERBB1\_DOWNSTREAM\_PATHWAY**: ErbB1 downstream signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_ERBB1\_DOWNSTREAM\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_ERBB1_DOWNSTREAM_PATHWAY.html)

**KEGG\_LEISHMANIA\_INFECTION**: Leishmania infection [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG\_LEISHMANIA\_INFECTION.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG_LEISHMANIA_INFECTION.html)

**REACTOME\_LEISHMANIA\_INFECTION**: Leishmania infection [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_LEISHMANIA\_INFECTION.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_LEISHMANIA_INFECTION.html)

**WP\_NEURAL\_CREST\_CELL\_MIGRATION\_DURING\_DEVELOPMENT**: Neural crest cell migration during development [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_NEURAL\_CREST\_CELL\_MIGRATION\_DURING\_DEVELOPMENT.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_NEURAL_CREST_CELL_MIGRATION_DURING_DEVELOPMENT.html)

**KOKKINAKIS\_METHIONINE\_DEPRIVATION\_96HR\_UP**: Genes up-regulated in MEWO cells (melanoma) after 96 h of methionine [PubChem=876] deprivation. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KOKKINAKIS\_METHIONINE\_DEPRIVATION\_96HR\_UP.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KOKKINAKIS_METHIONINE_DEPRIVATION_96HR_UP.html)

**KEGG\_ERBB\_SIGNALING\_PATHWAY**: ErbB signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG\_ERBB\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG_ERBB_SIGNALING_PATHWAY.html)

**WP\_ERBB\_SIGNALING\_PATHWAY**: ErbB signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_ERBB\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_ERBB_SIGNALING_PATHWAY.html)

**BIOCARTA\_STRESS\_PATHWAY**: TNF/Stress Related Signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_STRESS\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_STRESS_PATHWAY.html)

**KEGG\_PATHWAYS\_IN\_CANCER**: Pathways in cancer [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG\_PATHWAYS\_IN\_CANCER.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG_PATHWAYS_IN_CANCER.html)

**WP\_NETRIN\_UNC5B\_SIGNALING\_PATHWAY**: Netrin UNC5B signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_NETRIN\_UNC5B\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_NETRIN_UNC5B_SIGNALING_PATHWAY.html)

**WP\_NUCLEAR\_RECEPTORS\_META\_PATHWAY**: Nuclear receptors meta pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_NUCLEAR\_RECEPTORS\_META\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_NUCLEAR_RECEPTORS_META_PATHWAY.html)

**GARGALOVIC\_RESPONSE\_TO\_OXIDIZED\_PHOSPHOLIPIDS\_TURQUOISE\_UP**: Genes from the turquoise module which are up-regulated in HAEC cells (primary aortic endothelium) after exposure to the oxidized 1-palmitoyl-2-arachidonyl-sn-3-glycerophosphorylcholine (oxPAPC). [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/GARGALOVIC\_RESPONSE\_TO\_OXIDIZED\_PHOSPHOLIPIDS\_TURQUOISE\_UP.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/GARGALOVIC_RESPONSE_TO_OXIDIZED_PHOSPHOLIPIDS_TURQUOISE_UP.html)

**WP\_TOLL\_LIKE\_RECEPTOR\_SIGNALING\_PATHWAY**: Toll like receptor signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_TOLL\_LIKE\_RECEPTOR\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY.html)

**WP\_EGF\_EGFR\_SIGNALING\_PATHWAY**: EGF EGFR signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_EGF\_EGFR\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_EGF_EGFR_SIGNALING_PATHWAY.html)

**BOQUEST\_STEM\_CELL\_CULTURED\_VS\_FRESH\_UP**: Genes up-regulated in cultured stromal stem cells from adipose tissue, compared to the freshly isolated cells. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BOQUEST\_STEM\_CELL\_CULTURED\_VS\_FRESH\_UP.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BOQUEST_STEM_CELL_CULTURED_VS_FRESH_UP.html)

**WP\_ANDROGEN\_RECEPTOR\_SIGNALING\_PATHWAY**: Androgen receptor signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_ANDROGEN\_RECEPTOR\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_ANDROGEN_RECEPTOR_SIGNALING_PATHWAY.html)

**MARKS\_ACETYLATED\_NON\_HISTONE\_PROTEINS**: Non-histone proteins that are acetylated. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/MARKS\_ACETYLATED\_NON\_HISTONE\_PROTEINS.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/MARKS_ACETYLATED_NON_HISTONE_PROTEINS.html)

**PID\_CD40\_PATHWAY**: CD40/CD40L signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_CD40\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_CD40_PATHWAY.html)

**REACTOME\_DISEASES\_OF\_PROGRAMMED\_CELL\_DEATH**: Diseases of programmed cell death [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_DISEASES\_OF\_PROGRAMMED\_CELL\_DEATH.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_DISEASES_OF_PROGRAMMED_CELL_DEATH.html)

**WP\_PHYSICO\_CHEMICAL\_FEATURES\_AND\_TOXICITY\_ASSOCIATED\_PATHWAYS**: Physico chemical features and toxicity associated pathways [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_PHYSICO\_CHEMICAL\_FEATURES\_AND\_TOXICITY\_ASSOCIATED\_PATHWAYS.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_PHYSICO_CHEMICAL_FEATURES_AND_TOXICITY_ASSOCIATED_PATHWAYS.html)

**BIOCARTA\_PDGF\_PATHWAY**: PDGF Signaling Pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_PDGF\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_PDGF_PATHWAY.html)

**AMIT\_SERUM\_RESPONSE\_20\_MCF10A**: Genes whose expression peaked at 20 min after stimulation of MCF10A cells with serum. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/AMIT\_SERUM\_RESPONSE\_20\_MCF10A.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/AMIT_SERUM_RESPONSE_20_MCF10A.html)

**AMIT\_SERUM\_RESPONSE\_40\_MCF10A**: Genes whose expression peaked at 40 min after stimulation of MCF10A cells with serum. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/AMIT\_SERUM\_RESPONSE\_40\_MCF10A.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/AMIT_SERUM_RESPONSE_40_MCF10A.html)

**REACTOME\_DEVELOPMENTAL\_BIOLOGY**: Developmental Biology [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_DEVELOPMENTAL\_BIOLOGY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_DEVELOPMENTAL_BIOLOGY.html)

**KEGG\_TOLL\_LIKE\_RECEPTOR\_SIGNALING\_PATHWAY**: Toll-like receptor signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG\_TOLL\_LIKE\_RECEPTOR\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY.html)

**PID\_RAC1\_PATHWAY**: RAC1 signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_RAC1\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_RAC1_PATHWAY.html)

**REACTOME\_INTERLEUKIN\_17\_SIGNALING**: Interleukin-17 signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_INTERLEUKIN\_17\_SIGNALING.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_INTERLEUKIN_17_SIGNALING.html)

**BIOCARTA\_INSULIN\_PATHWAY**: Insulin Signaling Pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_INSULIN\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_INSULIN_PATHWAY.html)

**WP\_BMP\_SIGNALING\_IN\_EYELID\_DEVELOPMENT**: BMP signaling in eyelid development [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_BMP\_SIGNALING\_IN\_EYELID\_DEVELOPMENT.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_BMP_SIGNALING_IN_EYELID_DEVELOPMENT.html)

**REACTOME\_OXIDATIVE\_STRESS\_INDUCED\_SENESCENCE**: Oxidative Stress Induced Senescence [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_OXIDATIVE\_STRESS\_INDUCED\_SENESCENCE.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_OXIDATIVE_STRESS_INDUCED_SENESCENCE.html)

**WP\_T\_CELL\_RECEPTOR\_SIGNALING\_PATHWAY**: T cell receptor signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_T\_CELL\_RECEPTOR\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_T_CELL_RECEPTOR_SIGNALING_PATHWAY.html)

**KEGG\_T\_CELL\_RECEPTOR\_SIGNALING\_PATHWAY**: T cell receptor signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG\_T\_CELL\_RECEPTOR\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY.html)

**BIOCARTA\_TCR\_PATHWAY**: T Cell Receptor Signaling Pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_TCR\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_TCR_PATHWAY.html)

**PID\_PDGFRA\_PATHWAY**: PDGFR-alpha signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_PDGFRA\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_PDGFRA_PATHWAY.html)

**WP\_ESTROGEN\_RECEPTOR\_PATHWAY**: Estrogen receptor pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_ESTROGEN\_RECEPTOR\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_ESTROGEN_RECEPTOR_PATHWAY.html)

**PID\_P38\_ALPHA\_BETA\_DOWNSTREAM\_PATHWAY**: Signaling mediated by p38-alpha and p38-beta [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_P38\_ALPHA\_BETA\_DOWNSTREAM\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_P38_ALPHA_BETA_DOWNSTREAM_PATHWAY.html)

**WP\_APOPTOSIS**: Apoptosis [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_APOPTOSIS.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_APOPTOSIS.html)

**WEIGEL\_OXIDATIVE\_STRESS\_BY\_HNE\_AND\_H2O2**: Oxidative stress genes down-regulated in ARPE-19 cells (retinal pigmented epithelium) in response to HNE and H2O2 [PubChem=5283344;784]. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WEIGEL\_OXIDATIVE\_STRESS\_BY\_HNE\_AND\_H2O2.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WEIGEL_OXIDATIVE_STRESS_BY_HNE_AND_H2O2.html)

**WP\_MAPK\_CASCADE**: MAPK cascade [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_MAPK\_CASCADE.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_MAPK_CASCADE.html)

**REACTOME\_SIGNALING\_BY\_NOTCH**: Signaling by NOTCH [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_SIGNALING\_BY\_NOTCH.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_SIGNALING_BY_NOTCH.html)

**WP\_COPPER\_HOMEOSTASIS**: Copper homeostasis [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_COPPER\_HOMEOSTASIS.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_COPPER_HOMEOSTASIS.html)

**PID\_ILK\_PATHWAY**: Integrin-linked kinase signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_ILK\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_ILK_PATHWAY.html)

**WP\_TGF\_BETA\_SIGNALING\_PATHWAY**: TGF beta signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_TGF\_BETA\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_TGF_BETA_SIGNALING_PATHWAY.html)

**BIOCARTA\_FAS\_PATHWAY**: FAS signaling pathway ( CD95 ) [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_FAS\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_FAS_PATHWAY.html)

**BIOCARTA\_TOLL\_PATHWAY**: Toll-Like Receptor Pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_TOLL\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_TOLL_PATHWAY.html)

**WP\_NEUROINFLAMMATION**: Neuroinflammation [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_NEUROINFLAMMATION.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_NEUROINFLAMMATION.html)

**PID\_FAK\_PATHWAY**: Signaling events mediated by focal adhesion kinase [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_FAK\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_FAK_PATHWAY.html)

**BIOCARTA\_EGF\_PATHWAY**: EGF Signaling Pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_EGF\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_EGF_PATHWAY.html)

**WP\_CELL\_MIGRATION\_AND\_INVASION\_THROUGH\_P75NTR**: Cell migration and invasion through p75NTR [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_CELL\_MIGRATION\_AND\_INVASION\_THROUGH\_P75NTR.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_CELL_MIGRATION_AND_INVASION_THROUGH_P75NTR.html)

**WP\_TNF\_ALPHA\_SIGNALING\_PATHWAY**: TNF alpha signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_TNF\_ALPHA\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_TNF_ALPHA_SIGNALING_PATHWAY.html)

**WP\_TROP2\_REGULATORY\_SIGNALING**: TROP2 regulatory signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_TROP2\_REGULATORY\_SIGNALING.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_TROP2_REGULATORY_SIGNALING.html)

**REACTOME\_PTEN\_REGULATION**: PTEN Regulation [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_PTEN\_REGULATION.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_PTEN_REGULATION.html)

**PID\_PDGFRB\_PATHWAY**: PDGFR-beta signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_PDGFRB\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_PDGFRB_PATHWAY.html)

**PID\_ERBB2\_ERBB3\_PATHWAY**: ErbB2/ErbB3 signaling events [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_ERBB2\_ERBB3\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_ERBB2_ERBB3_PATHWAY.html)

**BIOCARTA\_IL2\_PATHWAY**: IL 2 signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_IL2\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_IL2_PATHWAY.html)

**REACTOME\_TOLL\_LIKE\_RECEPTOR\_TLR1\_TLR2\_CASCADE**: Toll Like Receptor TLR1:TLR2 Cascade [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_TOLL\_LIKE\_RECEPTOR\_TLR1\_TLR2\_CASCADE.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_TOLL_LIKE_RECEPTOR_TLR1_TLR2_CASCADE.html)

**WP\_PDGFR\_BETA\_PATHWAY**: PDGFR beta pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_PDGFR\_BETA\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_PDGFR_BETA_PATHWAY.html)

**WP\_BREAST\_CANCER\_PATHWAY**: Breast cancer pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_BREAST\_CANCER\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_BREAST_CANCER_PATHWAY.html)

**WP\_RANKL\_RANK\_SIGNALING\_PATHWAY**: RANKL RANK signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_RANKL\_RANK\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_RANKL_RANK_SIGNALING_PATHWAY.html)

**WP\_ESTROGEN\_SIGNALING\_PATHWAY**: Estrogen signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_ESTROGEN\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_ESTROGEN_SIGNALING_PATHWAY.html)

**REACTOME\_SIGNALING\_BY\_INTERLEUKINS**: Signaling by Interleukins [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_SIGNALING\_BY\_INTERLEUKINS.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_SIGNALING_BY_INTERLEUKINS.html)

**DACOSTA\_UV\_RESPONSE\_VIA\_ERCC3\_COMMON\_DN**: Common down-regulated transcripts in fibroblasts expressing either XP/CS or TDD mutant forms of ERCC3 [GeneID=2071], after UVC irradiation. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/DACOSTA\_UV\_RESPONSE\_VIA\_ERCC3\_COMMON\_DN.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/DACOSTA_UV_RESPONSE_VIA_ERCC3_COMMON_DN.html)

**REACTOME\_MAPK6\_MAPK4\_SIGNALING**: MAPK6/MAPK4 signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_MAPK6\_MAPK4\_SIGNALING.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_MAPK6_MAPK4_SIGNALING.html)

**BIOCARTA\_ETS\_PATHWAY**: METS affect on Macrophage Differentiation [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA\_ETS\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/BIOCARTA_ETS_PATHWAY.html)

**KEGG\_MAPK\_SIGNALING\_PATHWAY**: MAPK signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG\_MAPK\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/KEGG_MAPK_SIGNALING_PATHWAY.html)

**WP\_MAPK\_SIGNALING\_PATHWAY**: MAPK signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_MAPK\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_MAPK_SIGNALING_PATHWAY.html)

**PID\_SMAD2\_3NUCLEAR\_PATHWAY**: Regulation of nuclear SMAD2/3 signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_SMAD2\_3NUCLEAR\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_SMAD2_3NUCLEAR_PATHWAY.html)

**REACTOME\_TOLL\_LIKE\_RECEPTOR\_9\_TLR9\_CASCADE**: Toll Like Receptor 9 (TLR9) Cascade [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_TOLL\_LIKE\_RECEPTOR\_9\_TLR9\_CASCADE.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_TOLL_LIKE_RECEPTOR_9_TLR9_CASCADE.html)

**WP\_IL\_1\_SIGNALING\_PATHWAY**: IL 1 signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_IL\_1\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_IL_1_SIGNALING_PATHWAY.html)

**WP\_IL\_5\_SIGNALING\_PATHWAY**: IL 5 signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_IL\_5\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_IL_5_SIGNALING_PATHWAY.html)

**WP\_VEGFA\_VEGFR2\_SIGNALING**: VEGFA VEGFR2 signaling [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_VEGFA\_VEGFR2\_SIGNALING.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_VEGFA_VEGFR2_SIGNALING.html)

**REACTOME\_CYTOKINE\_SIGNALING\_IN\_IMMUNE\_SYSTEM**: Cytokine Signaling in Immune system [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME\_CYTOKINE\_SIGNALING\_IN\_IMMUNE\_SYSTEM.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/REACTOME_CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM.html)

**WP\_NEURAL\_CREST\_CELL\_MIGRATION\_IN\_CANCER**: Neural crest cell migration in cancer [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_NEURAL\_CREST\_CELL\_MIGRATION\_IN\_CANCER.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_NEURAL_CREST_CELL_MIGRATION_IN_CANCER.html)

**DACOSTA\_UV\_RESPONSE\_VIA\_ERCC3\_DN**: Genes down-regulated in fibroblasts expressing mutant forms of ERCC3 [GeneID=2071] after UV irradiation. [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/DACOSTA\_UV\_RESPONSE\_VIA\_ERCC3\_DN.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/DACOSTA_UV_RESPONSE_VIA_ERCC3_DN.html)

**PID\_IL1\_PATHWAY**: IL1-mediated signaling events [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID\_IL1\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/PID_IL1_PATHWAY.html)

**WP\_IL\_3\_SIGNALING\_PATHWAY**: IL 3 signaling pathway [[https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP\_IL\_3\_SIGNALING\_PATHWAY.html]](https://www.gsea-msigdb.org/gsea/msigdb/human/geneset/WP_IL_3_SIGNALING_PATHWAY.html)

The list of signatures has been truncated to include only signatures with the highest tissue association scores.

# 7. Gene Descriptions

**NCBI Gene Summary**: This gene is the putative transforming gene of avian sarcoma virus 17. It encodes a protein which is highly similar to the viral protein, and which interacts directly with specific target DNA sequences to regulate gene expression. This gene is intronless and is mapped to 1p32-p31, a chromosomal region involved in both translocations and deletions in human malignancies. [provided by RefSeq, Jul 2008]

**GeneCards Summary**: JUN (Jun Proto-Oncogene, AP-1 Transcription Factor Subunit) is a Protein Coding gene. Diseases associated with JUN include Breast Cancer and Sarcoma. Among its related pathways are MyD88 dependent cascade initiated on endosome and Prolactin Signaling. Gene Ontology (GO) annotations related to this gene include RNA binding and sequence-specific DNA binding. An important paralog of this gene is JUND.

**UniProtKB/Swiss-Prot Summary**: Transcription factor that recognizes and binds to the AP-1 consensus motif 5’-TGA[GC]TCA-3’ [PMID: 10995748, PMID: 22083952]. Heterodimerizes with proteins of the FOS family to form an AP-1 transcription complex, thereby enhancing its DNA binding activity to the AP-1 consensus sequence 5’-TGA[GC]TCA-3’ and enhancing its transcriptional activity. Together with FOSB, plays a role in activation-induced cell death of T cells by binding to the AP-1 promoter site of FASLG/CD95L, and inducing its transcription in response to activation of the TCR/CD3 signaling pathway [PMID: 12618758]. Promotes activity of NR5A1 when phosphorylated by HIPK3 leading to increased steroidogenic gene expression upon cAMP signaling pathway stimulation [PMID: 17210646]. Involved in activated KRAS-mediated transcriptional activation of USP28 in colorectal cancer (CRC) cells [PMID: 24623306]. Binds to the USP28 promoter in colorectal cancer (CRC) cells [PMID: 24623306]. Upon Epstein-Barr virus (EBV) infection, binds to viral BZLF1 Z promoter and activates viral BZLF1 expression.

# 8. Cellular Location of Gene Product

Nuclear expression in several tissues, mostly in a fraction of the cells. Mainly localized to the nucleoplasm. In addition localized to the micronucleus. Predicted location: Intracellular [<https://www.proteinatlas.org/ENSG00000177606/subcellular>]

# 9. Mechanistic Information

* Activation of c-Jun via JNK signaling contributes to stress-induced cell death in a variety of cell types. For example, treatment of Jurkat T cell line with UV, gamma irradiation, or anisomycin lead to prolonged JNK activation in parallel with FasL expression and cell death, indicating that FasL might be downstream target of c-Jun [PMID: 9551965]. Activation of c-Jun in sympathetic neurons in the absence of nerve growth factor (NGF) leads to cell death mediated by BIM(EL), a proapoptotic BCL-2 family member [PMID: 11301023].
* In human fibroblasts c-Jun promotes survival by negatively regulating the tumor-suppressor PTEN which leads to the activation of the Akt survival pathway [PMID: 16676006]. In human endothelial cells and mouse fibroblasts formation of c-Jun-ATF2 complex leads to activation of anti-apoptotic Bcl-XL protein [PMID: 20507983].
* Transforming growth factor beta 1 (TGF-beta 1) and razoxane induced maximal c-jun mRNA expression in human keratinocytes 4 days after treatment, concurrent with predifferentiation growth arrest (PGA). TGF-beta 1 maintained high c-jun mRNA levels even after 3 more days, indicating stable induction [PMID: 1419906].
* In JB6 cells, c-Jun mRNA expression was downregulated when cells entered a quiescent state due to reduced serum concentration. However, treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA) stimulated c-Jun expression and morphological changes, with varying expression levels in transformed cell foci [PMID: 7955078].

## Summary

The Jun gene, encoding the c-Jun protein, is a transcription factor that binds to the AP-1 consensus motif, modulating gene expression crucial for cell proliferation, differentiation, and apoptosis [CS: 9]. During conditions of stress or toxicity, such as UV exposure in skin, the upregulation of Jun enhances the transcriptional activity of AP-1 complexes that regulate genes responsible for cell survival and apoptosis [CS: 8]. For example, in fibroblasts c-Jun can promote cell survival through its negative regulation of tumor suppressor PTEN, leading to activation of the Akt pathway, which could serve as a defense mechanism against further damage [CS: 7].

In T-cells damaged with UV, gamma irradiation, or anisomycin, prolonged JNK activation leads to FasL expression and cell death, which may be a response to eliminate cells with potential UV-induced DNA damage [CS: 8].

# 10. Upstream Regulators

* On the protein level, stimulation of c-Jun by tumor promoter phorbol-ester (TPA), growth factors or stress stimulis factors can significantly enchance the DNA binding and transcription activity of c-Jun. The process is initiated by activated signal transduction cascades that lead to a rapid change in the phosphorylation state of c-Jun by JUN N-terminal kinase (JNK) group of mitogen-activated protein kinases (MAPK/JNK kinases) [PMID: 36253406]. These events takes place on the pre-existing c-Jun, within minutes of stimulus treatment, and is independent of de-novo protein synthesis [PMID: 1454848].
* In response to stress factors such as UV or H2O2, c-Jun expression is steadily elevated [PMID: 10540944]. This suggest that c-Jun serves as an early target for the signal transduction pathway elicited by DNA damage [PMID: 1901948]. Expression of c-Jun is regulated by NF-kappaB, sp1, CCAAT-binding transcription factors, and the its promoter contains a high-affinity AP-1 binding site. These observations suggest the existence of a regulatory circuit, in which AP-1 can activate the c-Jun promoter and gene expression, whereas, expression of c-Jun in turn further enhances AP-1 thereby potentiating its own gene promoter activation [PMID: 3142689]. As a result, c-Jun can efficiently convert transient biochemical signals to sustained AP-1 activity and act as a potent transcription factor to regulate long-lasting biological outcomes.
* The growth factor activity of plasminogen activators (PAs) is associated with a rapid transient activation of early response genes, c-fos, c-jun and c-myc, in human dermal fibroblasts [PMID: 10801075].
* SHARPIN regulates cell proliferation of cutaneous basal cell carcinoma via inactivation of the transcriptional factors GLI2 and c-JUN [PMID: 32319607].
* MITF suppresses c-Jun through binding to the c-Jun enhancer. c-Jun is critical for inflammation-induced dedifferentiation and the reciprocal gain of inflammatory responsiveness in melanoma cells [PMID: 26530832].
* AFF4 facilitates melanoma cell progression by regulating c-Jun activity [PMID: 33417923].
* The expression of the c-fos and c-jun genes were augmented in skin and muscle of transgenic mice carrying the human T-cell leukemia virus type-I tax gene [PMID: 7732661].
Augmentation of c-fos and c-jun gene expression was observed in histologically normal skin and muscle of transgenic mice carrying the human T-cell leukemia virus type-I tax gene [PMID: 7732661].
* There was lower expression of p38 and c-Jun at the mRNA and protein levels following concentrated growth factor (CGF) treatment in the UVA-induced photoaging of human dermal fibroblasts (HDFs) [PMID: 32627834].
* 17beta-estradiol suppresses carboxylesterases by activating c-Jun/AP-1 pathway in primary human and mouse hepatocytes [PMID: 29175444]

# 11. Tissues/Cell Type Where Genes are Overexpressed

**Tissue type enchanced**: low tissue specificity [<https://www.proteinatlas.org/ENSG00000177606/tissue>]

**Cell type enchanced**: ovarian stromal cells (cell type enhanced) [[https://www.proteinatlas.org/ENSG00000177606/single+cell+type](https://www.proteinatlas.org/ENSG00000177606/single%2Bcell%2Btype)]

# 12. Role of Gene in Other Tissues

* In patients with acute liver injury, c-Jun/AP-1 transcription factor is strongly expressed in the liver, as a target of c-Jun N-terminal kinase (JNK). In a mouse model using Con A for T cell-mediated hepatitis, hepatocyte-specific c-Jun knockout mice showed increased liver cell death and mortality, attributed to decreased inducible nitric oxide synthase (nos2) expression and reduced nitric oxide production [PMID: 17940019].
* In regenerating liver cells posthepatectomy, c-Jun mRNA is upregulated and forms complexes with c-Fos and liver-enriched regulatory factor-1 (LRF-1) [PMID: 1406655]. Elevation of c-Jun mRNA was observed following liver injury from carbon tetrachloride (CCl4) or galactosamine (GalN) [PMID: 8425910]. c-Jun expression in liver regeneration is mediated by TLR signaling pathways [PMID: 20936148].
* In human renal diseases, phosphorylated c-Jun (pc-Jun) was consistently present in glomerular and tubular cell nuclei. The level of pc-Jun expression correlated with various indicators of renal damage such as focal glomerulosclerosis, interstitial fibrosis, cell proliferation, KIM-1 expression, macrophage accumulation, and renal function impairment [PMID: 17891746].
* The mRNAs encoding c-Fos, c-Jun, Jun-D, and Jun-B were induced within 1 h of exposure to hypoxia in cardiac myocytes. These inductions coincided with loss in myocyte contractility but occurred before there was irreversible cell damage or significant ATP loss [PMID: 8344964]

# 13. Chemicals Known to Elicit Transcriptional Response of Biomarker in Tissue of Interest

## **Compounds that increase expression of the gene:**

* 1,2,4-trimethylbenzene [PMID: 17337753]
* 2-hydroxypropanoic acid [PMID: 30851411]
* aluminium oxide [PMID: 16488289]
* bis(2-chloroethyl) sulfide [PMID: 15674843]
* deoxynivalenol [PMID: 24937323, PMID: 32416088]
* mechlorethamine [PMID: 31639410]
* ochratoxin A [PMID: 23172667]
* paracetamol [PMID: 12540782, PMID: 32045647]
* patulin [PMID: 21964610]
* phorbol 13-acetate 12-myristate [PMID: 26100520, PMID: 17148446]
* rac-lactic acid [PMID: 30851411]
* undecane [PMID: 17337753]

## **Compounds that decrease expression of the gene:**

* sodium arsenite [PMID: 34032870]

# 14. DisGeNet Biomarker Associations to Disease in Organ of Interest

Most relevant biomarkers with lower score or lower probability of association with disease or organ of interest:

* Malignant neoplasm of breast [PMID: 10369069, PMID: 17637753, PMID: 20511396, PMID: 21384344, PMID: 22004728]
* Breast Carcinoma [PMID: 10369069, PMID: 11891846, PMID: 17458902, PMID: 17637753, PMID: 20511396]
* Carcinogenesis [PMID: 10924853, PMID: 16106402, PMID: 19435822, PMID: 19653276, PMID: 19671687]