**Supplementary Data**

**Supplementary Figure 1.** C-Jun N-terminal kinase (JNK) and insulin signaling after 20 min of cell treatment.Theimmortalized human brain endothelial cells (iHBEC) were treated with amyloid-β (Aβ)1-42 (10 µM), Aβscrambled (Aβsc) peptide (10 µM), insulin (1.7 µM), and SP600125 (25µM) alone, or insulin and SP600125 in combination with Aβ peptides for 20 min. Cell-proteins were resolved by SDS-PAGE, transferred to PVDF membrane and immunoblotted for c-Jun ser63 phosphorylation (A), insulin receptor phosphorylation (B) and AKT phosphorylation (C). The bands were semi-quantified by densitometry analysis and normalized to actin. The data from three separate experiments were averaged and presented relative to vehicle (One-way ANOVA, Bonferroni post-hoc test). Please note that not all the comparisons are shown within the p-cJun graph; all the treatments that were shown to be statistically significant to Aβ were also statistically significant to Ins+Aβ and Ins+Aβsc (except versus SP) treatments. Please note that not all the comparisons are shown within the p-AKT graph; all the treatments that are shown to be statistically significant to vehicle were also statistically significant to Aβ, Aβsc, SP, SP+Aβ, and SP+Aβsc treatments.

**Supplementary Figure 2.** The transcription factors (TFs) from the shared and divergent pathways of Aβ1-42 and insulin treatments were entered into the DAVID Bioinformatics Resource v 6.7. The included TFs were categorized into three clusters, cluster 1 (A), cluster 2 (B), and cluster 3 (C), based on functional classification. Green corresponds to the gene-term associating positively and black denotes that the gene-term association has not been reported. DAVID excluded the following TFs: NFkB, CBFB, SMAD3/4, AP-2, Stat-6, CREB-BP, GR/PR, Stat-5b, AR, PPAR, LF-A1, p53, CD28RC, EGR-2, and Myc. The following TFs were not inputted into DAVID because the Official Gene Name for these TFs has not been defined: EBP-80, MEF-1, KPF-1, and X2BP [[1-7](#_ENREF_1)]. Of note, the following so-called TFs actually name the DNA binding sequence and are not TFs *per se*: PO-B, MRE, HSE, DE-1, and ETS [[8-12](#_ENREF_8)].

**Supplementary Table 2.** TFs changing with insulin only.

|  |
| --- |
| **TFs increased relative to Aβsc** |
| **TF ID** | **Aβ** | **Ins** | **Aβ+Ins** | **Ins+Aβsc** |
| PTF-1b | 1.0 | 10.5 | 0.7 | 5.8 |
| SRY (1) | 1.5 | 9.4 | 8.1 | 11.6 |
| FKHR (1) | 1.8 | 8.0 | 5.1 | 13.2 |
| AFP-1 | 0.9 | 7.9 | 5.2 | 10.1 |
| LXRE-1 | 0.7 | 7.4 | 1.4 | 8.3 |
| MEF-2a | 1.3 | 6.4 | 11.4 | 8.1 |
| ORE | 0.8 | 5.9 | 3.0 | 8.2 |
| T3R | 0.7 | 5.6 | 0.6 | 3.9 |
| MAZ | 0.7 | 4.4 | 1.0 | 4.6 |
| PAX-2 (1) | 0.9 | 4.2 | 2.0 | 6.4 |
| EGF BP | 1.6 | 4.2 | 3.6 | 4.5 |
| SPERM-1 | 0.9 | 3.9 | 2.8 | 2.9 |
| HOXA-4 | 1.4 | 3.8 | 9.1 | 7.6 |
| SRE | 0.6 | 3.5 | 4.2 | 6.9 |
| KTP-1 | 1.3 | 3.5 | 4.0 | 4.0 |
| Ikaros | 1.4 | 3.3 | 2.1 | 3.0 |
| TCF/LEF | 0.6 | 3.0 | 2.4 | 3.2 |
| ELF | 0.6 | 2.9 | 2.0 | 2.5 |
| NF-E6/CP1 | 1.7 | 2.7 | 0.1 | 2.1 |
| FKHR (2) | 1.2 | 2.5 | 1.5 | 4.0 |
| NF-E2 (1) | 0.9 | 2.4 | 2.3 | 1.8 |
| NZF-3 | 1.1 | 2.4 | 1.8 | 2.9 |
| PAX-3 | 1.0 | 2.3 | 2.0 | 3.9 |
| MEF-3 | 1.2 | 2.3 | 1.1 | 3.0 |
| USF-1 (1) | 1.8 | 2.2 | 3.8 | 4.0 |
| ADR-1 | 1.6 | 2.2 | 1.9 | 2.7 |
| PPAR (1) | 1.4 | 2.1 | 2.3 | 3.0 |
| AF-1 | 0.7 | 2.1 | 1.1 | 2.4 |
| ANG-IRE | 0.7 | 2.0 | 1.6 | 2.7 |
| Tax/CREB | 0.5 | 2.0 | 1.4 | 2.3 |

**Table 3.** TFs changing with Aβ1-42 only.

|  |
| --- |
| **TFs increased relative to Aβsc** |
| **TF ID** | **Aβ** | **Ins** | **Aβ+Ins** | **Ins+Aβsc** |
| ABF-1 | 2.64 | 1.52 | 1.78 | 4.08 |
| Surf-2 (2) | 2.19 | 1.49 | 0.38 | 0.57 |
|   |   |   |   |   |
| **TFs decreased relative to Aβsc** |
| **TF ID** | **Aβ** | **Ins** | **Aβ+Ins** | **Ins+Aβsc** |
| Stat-1 | 0.01 | 1.70 | 1.72 | 1.81 |
| LSF | 0.02 | 1.05 | 0.31 | 0.70 |
| H4TF-1 | 0.02 | 0.95 | 0.65 | 0.67 |
| HFH-1 (2) | 0.03 | 1.08 | 0.90 | 1.12 |
| MyTI | 0.03 | 0.67 | 0.95 | 0.55 |
| LF-A2 | 0.03 | 1.05 | 0.75 | 0.74 |
| NF-1/L | 0.04 | 1.10 | 0.17 | 0.50 |
| E12/E7 | 0.05 | 0.92 | 0.77 | 0.99 |
| CEBP (3) | 0.05 | 1.22 | 0.78 | 1.39 |
| CSBP | 0.05 | 1.67 | 2.60 | 2.76 |
| WTI (3) | 0.05 | 1.29 | 0.66 | 1.20 |
| NFiL-2 | 0.06 | 1.61 | 0.93 | 1.41 |
| CP-1 | 0.06 | 0.66 | 0.70 | 0.44 |
| LH2/Lim-1 | 0.07 | 1.96 | 0.33 | 1.65 |
| SIF-1 | 0.07 | 1.22 | 0.78 | 1.43 |
| MyoG | 0.07 | 0.99 | 0.80 | 0.21 |
| LCR-F1 | 0.07 | 1.95 | 0.75 | 1.53 |
| PAX-1 | 0.09 | 1.49 | 0.97 | 0.89 |
| NF-1 (2) | 0.09 | 0.87 | 0.17 | 0.19 |
| ISGF | 0.09 | 1.32 | 0.06 | 0.76 |
| ATF (2) | 0.09 | 1.16 | 1.96 | 2.37 |
| GBF-1/2/3HY5 | 0.10 | 1.23 | 1.06 | 0.91 |
| PPAR (2) | 0.10 | 1.63 | 3.06 | 1.87 |
| PAX-2 (2) | 0.10 | 1.42 | 0.66 | 0.71 |
| HNF-4a | 0.10 | 0.95 | 0.18 | 1.08 |
| NF-A3 | 0.10 | 1.59 | 0.51 | 1.14 |
| ODC | 0.10 | 1.56 | 1.05 | 0.96 |
| IsI-1 | 0.11 | 1.70 | 1.70 | 1.35 |
| Ets/PEA3 (1) | 0.11 | 1.05 | 5.79 | 3.97 |
| ICSBP | 0.11 | 0.90 | 0.57 | 1.57 |
| HOXD-8 (2) | 0.12 | 1.19 | 1.23 | 0.75 |
| AML-1 | 0.12 | 0.95 | 1.35 | 1.05 |
| TGT-3 | 0.12 | 1.01 | 0.40 | 0.05 |
| ATF adelta | 0.13 | 0.67 | 0.85 | 0.27 |
| PPUR (2) | 0.13 | 1.19 | 0.80 | 0.08 |
| OCT (3) | 0.13 | 0.83 | 0.09 | 0.10 |
| NF-Y (2) | 0.13 | 0.99 | 0.70 | 0.60 |
| p53 (3) | 0.14 | 1.63 | 0.75 | 2.28 |
| TREF-1/2 | 0.15 | 1.00 | 0.90 | 0.11 |
| alpha-PAL | 0.15 | 1.52 | 0.91 | 0.03 |
| MDBP (2) | 0.15 | 0.97 | 0.37 | 1.27 |
| NCAM BP | 0.17 | 1.00 | 0.72 | 0.59 |
| ATF/CRE | 0.17 | 0.70 | 1.46 | 3.06 |
| GATA-1 (2) | 0.18 | 0.70 | 0.27 | 0.25 |
| CEBP (2) | 0.18 | 1.08 | 0.61 | 1.73 |
| RIPE3a1 | 0.18 | 1.11 | 0.89 | 1.10 |
| HOXD-8 (1) | 0.19 | 1.13 | 1.65 | 0.44 |
| TIF-1 | 0.19 | 1.61 | 0.78 | 0.03 |
| TCE | 0.21 | 1.04 | 0.79 | 1.62 |
| SP-1/ASP | 0.23 | 0.87 | 0.87 | 0.97 |
| Pur-1 | 0.23 | 1.09 | 0.84 | -0.01 |
| Bm-3 | 0.24 | 0.94 | 0.55 | 0.39 |
| c-Myc | 0.25 | 1.24 | 0.59 | 0.05 |
| CDP | 0.25 | 0.59 | 1.63 | 0.12 |
| SRF SAP | 0.27 | 1.28 | 0.44 | 4.49 |
| LyF (2) | 0.27 | 1.51 | 1.24 | 2.15 |
| MDBP (1) | 0.27 | 1.64 | 0.10 | 1.51 |
| RB | 0.27 | 0.83 | 1.11 | 1.33 |
| CdxA/NKX2 | 0.27 | 1.00 | 2.05 | 11.82 |
| b M globfactor B1 | 0.27 | 0.71 | 0.72 | 0.35 |
| NF-Gma (1) | 0.28 | 0.75 | 0.80 | 0.96 |
| XBP-1 X2 BP | 0.29 | 0.72 | 0.93 | 0.36 |
| Lactoferrin BP | 0.32 | 1.30 | 0.83 | 0.89 |
| X2 BP | 0.32 | 0.75 | 0.75 | 0.06 |
| CD28RC (2) | 0.32 | 1.96 | 0.95 | 0.50 |
| Myc-Max | 0.32 | 0.73 | 0.44 | 1.72 |
| ARP | 0.32 | 0.85 | 1.20 | 1.49 |
| ATF-a | 0.35 | 0.76 | 0.77 | 0.35 |
| v-Maf | 0.35 | 0.94 | 1.73 | 0.14 |
| LR-1 | 0.37 | 1.31 | 1.17 | 0.42 |
| RREB (1) | 0.38 | 0.99 | 1.40 | 2.09 |
| Cdx-2 | 0.38 | 0.94 | 0.43 | 1.08 |
| AP-3 (2) | 0.39 | 0.67 | 0.78 | 0.28 |
| msx-1/2/3 | 0.39 | 1.99 | 0.44 | 0.18 |
| N-ras BP | 0.39 | 1.58 | 0.79 | 1.31 |
| MTF (1) | 0.40 | 1.02 | 1.08 | 0.47 |
| CYP1A1 | 0.41 | 0.98 | 0.93 | 0.85 |
| AREB-6 | 0.41 | 0.90 | 2.04 | 3.42 |
| AP-2 (2) | 0.43 | 1.50 | 0.62 | 0.15 |
| ZNF174 | 0.43 | 1.22 | 1.34 | 2.10 |
| MEF-2 (1) | 0.48 | 1.97 | 0.00 | 5.53 |
| HiNF/D3 | 0.48 | 0.78 | 0.97 | 1.24 |
| Stat-4 | 0.50 | 1.77 | 1.67 | 2.88 |

**Table 4.** TF description and its reported involvement with JNK, insulin, or Alzheimer’s disease (AD).

|  |  |  |  |
| --- | --- | --- | --- |
| **TF Name & Description** | **Relationship with JNK** | **Relationship with Insulin** | **Relationship with AD** |
| **ADR-1**Alcohol dehydrogenase generegulator 1.Required for transcription of the glucose-repressed gene ADH2, and of genes required for ethanol, glycerol, and fatty acid utilization1. | Unknown | Adr1 augments the expression of several genes for fatty acid oxidation; Increased transcripts of Adr1 under biotin starvation (reminiscent of insulin resistance) [[13](#_ENREF_13)]. | • One of the major predicted transcription factor-binding sites for naturally occurring polymorphic variants in APP genes; The APP promoter sequence has at least 69 ADR1 consensus binding sites distributed evenly over 5.8 kb of length [[14](#_ENREF_14)].• ADR1 interacts with a down-stream positive element to activate PS1 transcription [[15](#_ENREF_15)]. |
| **AF-1**Also known as PSMD4.26S proteasome non-ATPase regulatory subunit 4 [[16](#_ENREF_16)]. | Unknown | Unknown | • AF-1 has been shown to interact with several apolipoprotein genes [[17](#_ENREF_17)].• Mutant ubiquitins (Ub+1 and Ub5+1) are refractory to processing by the 19S regulatory complex and are associated with AD [[16](#_ENREF_16)]. |
| **AFP-1**ABI five binding protein. Also known as Ninja-family protein AFP11. Acts as a negative regulator of abscisic acid (ABA) response during germination through the ubiquitin-mediated proteolysis of ABI5/DPBF12.  | Unknown | Unknown | Unknown |
| **Alpha-PAL**Also known as nuclear respiratory factor 1 (NRF1)1.  Homodimerizes and activates the expression of genes regulating cellular growth, respiration, heme biosynthesis, and mitochondrial DNA transcription and replication 1.  | • IL-6 treatment lead to increased NRF1 mRNA levels [[18](#_ENREF_18)].• Nrf1, Nrf2, c-Jun, JunB, FosB, c-Fos, Fra1, and Fra2 are components of the GP5 EpRE/protein complex after HNE exposure in L2 cells, and the increased nuclear content of Nrf1, Nrf2, and c-Jun is mediated through both ERK and p38MAPK pathways [[19](#_ENREF_19)].  | Prolonged Nrf1 overexpression triggers adipocyte inflammation and insulin resistance [[20](#_ENREF_20)]. | Unknown |
| **AML-1**Acute myeloid leukemia 1 protein. Also known as runt-related transcription factor (RUNX1).• Regulates the differentiation of hematopoietic stem cells into mature blood cells 3. | • AML1-ETO over-expression in leukemic U937 cells activated JNK, while SP600125 effectively abrogated AML1-ETO-induced Cx43 expression, indicating that JNK signaling pathway contributes to AML1-ETO induced Cx43 expression [[21](#_ENREF_21)]. • AML1-ETO transactivates the human c-jun promoter through the proximal AP-1 site by activating the JNK pathway [[22](#_ENREF_22)]. | mRNA expression of insulin-like growth factor-binding protein 3 (IGFBP-3) is downregulated by Runx1 [[23](#_ENREF_23)]. | SNPs variants within RUNX1 genes were strongly associated with AD[[24](#_ENREF_24)]. |
| **ANG-IRE**Angiotensinogen (ANG) insulin-response element (IRE). | Unknown | High glucose activates ANG expression and insulin inhibits this activation [[25](#_ENREF_25)]. | Unknown |
| **AP-1**Activator protein 1.Heterodimeric protein composed of proteins belonging to the c-Fos, c-Jun, ATF and JDP families; Regulates gene expression in response to a variety of stimuli including cytokines, growth factors, stress and bacterial and viral infections3.  | AP-1 is also known as jun protooncogene JUN, c-Jun 1. JNK is the c-Jun NH2-terminal kinase.  |  |  |
| **AP-2**Activator protein 2. AP-2 regulates gene expression during early development [[26](#_ENREF_26)].  | Activated JNK has been documented to decrease AP-2 binding in porcine aortic endothelial cells [[27](#_ENREF_27)]. | • JNK has roles in metabolic regulation of insulin resistance [[28](#_ENREF_28)].• Akt negatively regulates the JNK pathway in PC12 cells [[29](#_ENREF_29)].• Activation of JNK/stress-activated protein kinase by insulin [[30](#_ENREF_30)].• JNK Expression by macrophages promotes obesity-induced insulin resistance and Inflammation[[31](#_ENREF_31)]• JNK activation mediates islet amyloid-induced β-cell apoptosis in cultured human islet amyloid polypeptide transgenic mouse islets [[32](#_ENREF_32)].• AP-1 phosphorylates S307 of the IRS subunit inhibiting insulin signaling [[33](#_ENREF_33)]. | AP-2 is involved in inflammation, cell death, DNA repair and cell proliferation [[33](#_ENREF_33)]. |
| **AR**Androgen receptor  | JNK/c-jun pathway in AR-mediated up-regulation of human CYP27A1 (enzyme with several important roles in cholesterol homeostasis and vitamin D₃) [[34](#_ENREF_34)].  | • One of the known target genes of AR activation is insulin-like growth factor I (IGF-1) [[35](#_ENREF_35)].• AR- knockout mice demonstrate that AR deficiency results in the development of insulin resistance in males [[36](#_ENREF_36)].• Neuronal AR regulates hypothalamic insulin signalling by repressing NF-κB-mediated induction of protein-tyrosine phosphatase 1B (PTP1B). Hypothalamic insulin resistance leads to hepatic insulin resistance, lipid accumulation, and visceral obesity [[37](#_ENREF_37)]. | • Androgen regulates the seladin-1/DHCR24 gene ((SELective Alzheimer Disease INdicator-1)/DHCR24) [[38](#_ENREF_38)]. • Reduced androgen levels in aged men and women might be risk factors for age-related cognitive decline and AD [[39](#_ENREF_39)]. • Androgen regulation of Aβ involves an AR-dependent mechanism requiring up-regulation of the Aβ catabolizing enzyme NEP [[40](#_ENREF_40)]. |
| **AREB-6**Also known as zinc finger E-box binding homeobox 1 (ZEB1)Likely plays a role in transcriptional repression of IL-21.  | Small proline-rich protein 1B (SPRR1B) is up-regulated by the proinflammatory cytokines IL-1β and IFN-γ via p38 MAPK-mediated signalling pathways that lead to the activation of TFs CREB and ZEB1 [[41](#_ENREF_41)]. | IGF-I up-regulates ZEB1 expression in prostate cancer cells exhibiting an epithelial phenotype [[42](#_ENREF_42)]. | Unknown |
| **ARP**ApoAI regulatory protein-1. Also known as NR2F2Member of the steroid thyroid hormone superfamily of nuclear receptors; A ligand-inducible TF that is involved in the regulation of many different genes. Alternate splicing results in multiple transcript variants 1. | Unknown | • Insulin represses NR2F2 gene expression in pancreatic β-cells [[43](#_ENREF_43)].• The rs3743462 polymorphism affects glucose-responsive NR2F2 promoter regulation and thereby may influence whole-body insulin sensitivity [[43](#_ENREF_43)]. | The involvement of ARP-1 in the regulation of apoAI gene expression suggests that it may participate in lipid metabolism and cholesterol homeostasis [[44](#_ENREF_44)]. |
| **ATF**Also known as glial cell derived neurotrophic factor (GDNF). Highly conserved neurotrophic factor. Shown to promote the survival and differentiation of dopaminergic neurons in culture, and was able to prevent apoptosis of motor neurons induced by axotomy1. | • Activation of JNK, ERKs and p38 MAPK was observed in the GDNF-treated cells. Functional studies showed that the activation of these MAPKs was critical for Hs683 cell migration induced by GDNF [[45](#_ENREF_45)].• IL-1β stimulates GDNF release through the pathways of IκB-nuclear factor κB, p38 MAP kinase, p44/p42 MAP kinase and JAK-STAT3, but not through the SAPK/JNK pathway in glioma cells [[46](#_ENREF_46)]. | • GDNF influences β-cell development [[47](#_ENREF_47)]• PI3-kinase/Akt pathway plays a positive role in FGF-2-stimulated GDNF release independently of p44/p42 MAP kinase or SAPK/JNK in C6 glioma cells [[48](#_ENREF_48)]. • GDNF has beneficial effects on human islet survival and could be used to improve islet post-transplantation survival [[49](#_ENREF_49)]. | • Novel GDNF isoforms and cis-antisense GDNFOS gene linked to AD [[50](#_ENREF_50)].• GDNF levels in CSF of patients with early AD are increased [[51](#_ENREF_51)].• GDNF protect neuronal cell death in several neurodegenerative models, both *in vitro* and *in vivo* [[52](#_ENREF_52)]. |
| **Bm-3** | Unknown | Unknown | Unknown |
| **bM Globfactor B1** | Unknown | Unknown | Unknown |
| **CBFB**CCAAT-binding factor (CBF) subunit B [[53](#_ENREF_53)]. | Unknown | Unknown | Unknown |
| **CD28RC**CD28-responsive complex [[54](#_ENREF_54)].Essential for T-cell proliferation and survival, cytokine production, and T-helper type-2 development1.  | • B7-H4 inhibits T-cell proliferation and IL-2 production through interfering with activation of ERK, JNK, and AKT [[55](#_ENREF_55)].• Stimulation of CD28 induced AKT, JNK and ERK phosphorylation [[56](#_ENREF_56)]. | Unknown | The effect of Aβ peptides on the immune system of AD patients is a consequence of an unspecific modulation of the cell cycle dynamics and cytokine production by T cells, occurring simultaneously in a huge proportion of Aβ-exposed T lymphocytes and affecting immune system performance [[57](#_ENREF_57)]. |
| **CDP**CCAAT displacement protein.TF for many cellular and viral genes involved in differentiation, development, and proliferation [[58](#_ENREF_58)].  | Unknown | Unknown | Unknown |
| **Cdx-2**Major regulator of intestine-specific genes involved in cell growth and differentiation; Also plays a role in early embryonic development of the intestinal tract; Aberrant expression of this gene is associated with intestinal inflammation and tumorigenesis1.  | Unknown | • Involved in regulation of insulin secretion 4. • Transactivator of proglucagon and pro-insulin genes [[59](#_ENREF_59)]. • Activated expression accompanied by elevated insulin mRNA expression, and insulin synthesis; Bound to the insulin gene promoter enhancer elements [[60](#_ENREF_60)]. | Strong association with AD found at a promoter SNP rs11568820, which resides within Cdx-2 binding site. The risk-allele at rs11568820 is associated with lower VDR promoter activity [[61](#_ENREF_61)]. |
| **CEBP**CCAAT/enhancer binding protein. Modulates the expression of the leptin gene, a protein that plays an important role in body weight homeostasis; Interacts with CDK2 and CDK4, thereby inhibiting these kinases and causing growth arrest in cultured cells1. | Unknown | Unknown | Unknown |
| **c-Myc**Multifunctional, nuclear phosphoprotein involved in cell cycle progression, apoptosis and cellular transformation. Mutations, over-expression, rearrangement and translocation of c-Myc have been associated with a variety of hematopoietic tumors, leukemias and lymphomas1.  | • JNK phosphorylates and regulates the activity of c-Myc [[62](#_ENREF_62)].• Over-expression of c-Myc in HEK293 cells increases the levels of MAP4K1, MAP4K1 promoter activity, and phospho-c-Jun; Activation of β-catenin/Tcf dependent transcription in Pdcd4 knockdown cells up-regulates MAP4K1 expression and AP-1 activity via c-Myc [[63](#_ENREF_63)]. | Hyperinsulinemia may promote c-Myc signalling in breast cancer [[64](#_ENREF_64)]. | • Cell cycle activation by c-Myc leads to neuronal cell death; Induction of c-Myc by neurotoxic agents, or other disease factors, might be a key mediator in cell cycle activation and consequent cell death that is a feature of neurodegenerative diseases [[65](#_ENREF_65)].• Neuronal expression of Myc causes a neurodegenerative phenotype in a transgenic mouse [[66](#_ENREF_66)]. |
| **CP-1**Cysteine proteinase-11.  | Unknown | Unknown | Unknown |
| **CREB-BP**Cyclic AMP-response element binding protein. Ubiquitously expressed; Involved in the transcriptional co-activation of many different TFs; Plays critical roles in embryonic development, growth control, and homeostasis; Has histone acetyltransferase activity; Acts as a scaffold to stabilize additional protein interactions with the transcription complex; Acetylates non-histone proteins as well 1.  | Down-stream effector molecules of MAPKs [[67](#_ENREF_67)]. | • B-cell translocation gene-2 (BTG2) is a crucial cofactor in hepatic gluconeogenesis via upregulation of CREB in hepatocytes [[68](#_ENREF_68)]. • IRS-2 expression is stimulated by CREB-BP [[69](#_ENREF_69)].• Activation and regulation of GH gene expression requires the binding of POU1F1 to the GH promoter along with CREB-BP – its role as a target of IGF-1R signaling [[70](#_ENREF_70)]. | • BACE1 reduces CREB-BP phosphorylation; BACE1 may contribute to the memory and cognitive deficits typical of AD by regulating the cAMP/PKA/CREB pathway [[71](#_ENREF_71)].• Specific down-regulation of a subset of CREB-dependent genes, including c-fos, Bdnf and Nr4a2, were observed in the hippocampus of memory-impaired APP(Sw,Ind) transgenic mice [[72](#_ENREF_72)].• CREB-BP phosphorylation: a mechanistic marker in the development of memory enhancing AD therapeutics [[73](#_ENREF_73)].• Increasing CREB-BP function in the CA1 region of dorsal hippocampus rescues the spatial memory deficits in a mouse model of AD [[74](#_ENREF_74)].• Down-regulation of CREB-BP expression in AD brain and in Aβ-treated rat hippocampal neurons [[75](#_ENREF_75)]. |
| **CSBP**Also known as mitogen-activated protein kinase14 (MAPK14)Activated by various environmental stresses and proinflammatory cytokines; Roles in stress related transcription and cell cycle regulation and genotoxic stress response1.  | Unknown | Involved in regulation of insulin signaling 4.  | A novel p38 alpha MAPK inhibitor suppresses brain pro-inflammatory cytokine up-regulation and attenuates synaptic dysfunction and behavioral deficits in an AD mouse model [[76](#_ENREF_76)]. |
| **CYP1A1**Cytochrome P450, family 1, subfamily A, polypeptide 1. The cytochrome P450 proteins are monooxygenases which catalyze many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids; CYP1A1 localizes to the ER and its expression is induced by some polycyclic aromatic hydrocarbons (PAHs) 1.  | • SP600125 is a partial agonist of human aryl hydrocarbon receptor and induces CYP1A1 and CYP1A2 genes in primary human hepatocytes [[77](#_ENREF_77)].• TCDD-stimulated MAPKs were critical for the induction of AHR-dependent gene transcription and CYP1A1 expression [[78](#_ENREF_78)]. | • 1-NP-induced Cyp1a1 mRNA stabilization was mediated by Akt [[79](#_ENREF_79)]. •Insulin involved in modulation of CYP1A1 expression [[80](#_ENREF_80)]. | Involved in metabolism of drugs for AD [[81](#_ENREF_81)]. |
| **DE-1**Element from albumin gene 5. | Unknown | Unknown | Unknown |
| **E12/E47**E12/E47 is required for B and T lymphocyte development 1.  | Unknown | Unknown | Unknown |
| **E2F-1**Crucial role in the control of cell cycle and action of tumor suppressor proteins; Binds preferentially to retinoblastoma protein pRB in a cell-cycle dependent manner; Mediates both cell proliferation and p53-dependent/independent apoptosis 1. | • Macrophage inhibitory cytokine-1 stimulates proliferation of human umbilical vein endothelial cells by up-regulating cyclins D1 and E through the PI3K/Akt-, ERK-, and JNK-dependent AP-1 and E2F activation signaling pathways [[82](#_ENREF_82)].• The ASK1-JNK/p38 pathway does not appear to play a crucial role in E2F-1-induced apoptosis [[83](#_ENREF_83)].  | • IL-1β suppresses prolonged Akt activation and expression of E2F-1 and cyclin A in breast cancer cells [[84](#_ENREF_84)].• TNF-α inhibits cyclin A expression and retinoblastoma hyperphosphorylation triggered by IGF-I induction of new E2F-1 synthesis [[85](#_ENREF_85)].• E2F-1 overexpression in cardiomyocytes induces downregulation of p21CIP1 and p27KIP1 and release of active cyclin-dependent kinases in the presence of IGF-1 [[86](#_ENREF_86)]. | • Inhibition of ataxia telangiectasia-p53-E2F-1 pathway in neurons as a target for the prevention of neuronal apoptosis [[87](#_ENREF_87)].• Implication of E2F-1 in the modulation of neuronal apoptosis [[88](#_ENREF_88)].• Hyperphosphorylation of the retinoblastoma gene product and altered subcellular distribution of E2F-1 during AD and amyotrophic lateral sclerosis [[89](#_ENREF_89)]. • Up-regulation of E2F-1 in Down's syndrome brain exhibiting neuropathological features of AD-type dementia [[90](#_ENREF_90)].  |
| **EBP-80** Enhancer-binding protein-80 [[1](#_ENREF_1)]. | Unknown | Unknown | Unknown |
| **EGF BP**Epidermal growth factor. Synthesized as a large precursor molecule and proteolytically cleaved to generate the 53-amino acid epidermal growth factor peptide; Acts a potent mitogenic factor that plays an important role in the growth, proliferation and differentiation of numerous cell types; Acts by binding the epidermal growth factor receptor 1. | EGF can induce MAPK/JNK-mediated signal [[91](#_ENREF_91)]. | • EGF, insulin and IGF-1 have a common stimulatory effect on ENaC mediated by ROS production [[92](#_ENREF_92)].• NGF withdrawal causes apoptosis by decreasing EGF, NGF and insulin secretion from β cells of hyperglycemic rats [[93](#_ENREF_93)]. | • EGF receptor is a preferred target for treating Aβ-induced memory loss [[94](#_ENREF_94)].• Central role of the EGF receptor in neurometabolic aging [[95](#_ENREF_95)].• Matrix Metalloproteinase-2 and EGF are Decreased in Platelets of AD patients [[96](#_ENREF_96)]. |
| **EGR-2**Early growth response1. TF with three tandem C2H2-type zinc fingers. Defects in this gene are associated with Charcot-Marie-Tooth disease [[97](#_ENREF_97)]. | Unknown | Unknown | Unknown |
| **EKLF**Erythroid Kruppel-like factor [[98](#_ENREF_98)]. Hematopoietic-specific TF that induces high-level expression of adult β-globin and other erythroid genes1. | Unknown | Unknown | Unknown |
| **ELF**E74-like factor 15.  | Unknown | Unknown | Unknown |
| **ETS**response element | Unknown | Unknown | Unknown |
| **Ets/PEA3**Phosphatidylinositol-4-phosphate 5-kinase and related FYVE finger-containing proteins Signal transduction mechanisms1.  | uPA-invasive phenotype appears to require the activation of Ets/PEA3 and c-Jun transcription factors activated by the ERK and JNK pathways [[99](#_ENREF_99)].  | Unknown | Unknown |
| **FKHR**Also known as forkhead box O1 (FOXO1). May play a role in myogenic growth and differentiation; Translocation with PAX3 has been associated with alveolar rhabdomyosarcoma1.  | Foxo1 bridges the JNK pathway and the TF PDX-1 through its intracellular translocation [[100](#_ENREF_100)]. | • Correlation exists between FOXO1a (FKHR) and FOXO3a (FKHRL1) binding and the inhibition of basal glucose-6-phosphatase catalytic subunit gene transcription by insulin [[101](#_ENREF_101)].• High expression of PAX3-FKHR and IGF-II in ARMS synergistically play a key role in oncogenesis and tumor progression of ARMS [[102](#_ENREF_102)]. • Insulin-like growth factor-I induces the phosphorylation and nuclear exclusion of forkhead transcription factors in human neuroblastoma cells [[103](#_ENREF_103)].• May be involved in insulin resistance mechanisms [[104](#_ENREF_104)]. | Unknown |
| **GATA-1**Plays an important role in erythroid development by regulating the switch of fetal hemoglobin to adult haemoglobin1.  | Unknown | GATA motifs in the proximal exon 1 promoter of the rat insulin-like growth factor I gene [[105](#_ENREF_105)]. | Deletion of GATA showed that it could be involved in the regulation of BACE1 transcription [[106](#_ENREF_106)]. |
| **GBF-1/2/3HY5**Golgi brefeldin A resistant guanine nucleotide exchange factor 1. Regulates the recruitment of proteins to membranes by mediating GDP to GTP exchange; Localized to the Golgi apparatus and plays a role in vesicular trafficking by activating ADP ribosylation factor 1; Identified as an important host factor for viral replication1. | Unknown | Unknown | Unknown |
| **GKLF**Also known as Kruppel-like factor 4 (KLF4)1.  | Unknown | • KLF4 positively regulates human ghrelin expression [[107](#_ENREF_107)].• The Krüppel-like factor KLF15 regulates the insulin-sensitive glucose transporter GLUT4 [[108](#_ENREF_108)]. | Unknown |
| **GR/PR**Glucocorticoid receptor (GR); Progesterone receptor (PR)3; GR is also known as NR3C1 (nuclear receptor subfamily 3, group C, member 1); PR is also known as NR3C3 (nuclear receptor subfamily 3, group C, member 3)3. GR is the receptor to which cortisol and other glucocorticoids bind; GR affect genes controlling the development, metabolism, and immune response; PR is activated by the steroid hormone progesterone 3.  | P38 mitogen-activated protein kinase mediates GR function induced by dexamethasone in acute lymphoblastic leukemia cells [[109](#_ENREF_109)].  |  Responds to insulin stimulus 1.  | Unknown |
| **H4TF-1**Histone 4 binding protein5.  | Unknown | Unknown | Unknown |
| **HFH-1**Also known as forkhead box Q1 (FOXQ1).FOX genes are involved in embryonic development, cell cycle regulation, tissue-specific gene expression, cell signaling, and tumorigenesis1. | Unknown | Unknown | Unknown |
| **HiNF/D3**histone H35.  | Histone H3 Ser10 (H3S10) is a substrate for JNK, and JNK-bound promoters are enriched for H3S10 phosphorylation; Inhibition of JNK signaling in post-mitotic neurons reduces phosphorylation at H3S10 and the expression of target genes [[110](#_ENREF_110)] | Unknown | • Activation of stress-related signaling pathways could result in the increased transcription of APP, BACE1, and PS1 genes through DNMT-dependent hypomethylation and histone H3 hyperacetylation, thus leading to Aβ overproduction [[111](#_ENREF_111)].• Histone acetylation is significantly lower in AD temporal lobe than found in aged controls [[112](#_ENREF_112)]. |
| **HNF-4a**Hepatocyte nuclear factor 4, alpha, Nuclear TF which binds DNA as a homodimers; May play a role in development of the liver, kidney, and intestines; Mutations in this gene have been associated with monogenic autosomal dominant non-insulin-dependent diabetes mellitus type I 1.  | IL-1β reduces hepatic SHBG production by decreasing HNF-4α via MEK-1/2 and JNK MAPK pathways [[113](#_ENREF_113)]. | • Involved with diabetes type 1 [[114](#_ENREF_114)]. • Mutations in HNF-4alpha gene are associated with one form of maturity-onset diabetes of the young [[115](#_ENREF_115)]. | Unknown |
| **HOXA-4**Homeobox A4TF which may regulate gene expression, morphogenesis, and differentiation 1.  | Unknown | Unknown | Unknown |
| **HOXD-8**Homeobox D8Deletions that remove the entire HOXD gene cluster have been associated with severe limb and genital abnormalities; May play a role during embryogenesis and adult urogenital tract function 1.  | Unknown | Unknown | Unknown |
| **HSE**Heat shock consensus element 5.  | Unknown | Unknown | Heat shock factor-1 mediates the transcriptional activation of APP gene in response to stress [[116](#_ENREF_116)]. |
| **ICSBP**Interferon regulatory factor 8. TF of the interferon (IFN) regulatory factor (IRF) family; The IRF family proteins regulate expression of genes stimulated by type I IFNs, namely IFN-α and IFN-β 1. | Unknown | Unknown | Unknown |
| **ISGF**Interferon-Stimulated Response factor 5.  | Unknown | Unknown | Unknown |
| **Isl-1**Insulin gene enhancer protein Binds to the enhancer region of the insulin gene, among others; May play an important role in regulating insulin gene expression; Central to the development of pancreatic cell lineages and may also be required for motor neuron generation; Mutations in this gene have been associated with maturity-onset diabetes of the young 1. | Unknown | • ISL1 is essential for pancreatic islet cell and dorsal mesenchyme development; Mutations in ISL1 are associated with maturity-onset diabetes of the young and type 2 diabetes [[117](#_ENREF_117)]. • Regulation of insulin secretion 4. | Unknown |
| **KPF-1**Keratinocyte-Specific Transcription Factor, KRF-1 5.  | Unknown | Unknown | Unknown |
| **KTP-1**Keratinocyte transcriptional protein-1 5.  | Unknown | Unknown | Unknown |
| **Lactoferrin BP** | Requirement of the JNK-associated Bcl-2 pathway for human lactoferrin-induced apoptosis in the Jurkat leukemia T cell line [[118](#_ENREF_118)]. | LF regulates activity of insulin-like growth factor (IGF) [[119](#_ENREF_119)]. | Deposition of lactoferrin in fibrillar-type senile plaques in the brains of transgenic mouse models of AD [[120](#_ENREF_120)]. |
| **LCR-F1**Also known as nuclear factor (erythroid-derived 2)-like 1 (NFE2L1).Involved in globin gene expression in erythrocytes 1.  | Unknown | Unknown | Unknown |
| **LF-A1**Liver-specific factor A1Also known as HNF-4 [[121](#_ENREF_121)]. | c-Jun inhibits HNF4-alpha [[122](#_ENREF_122)]. | HNF-4 is insulin stimulated [[123](#_ENREF_123)]. | Unknown |
| **LF-A2**Liver-specific factors stimulate *in vitro* transcription from the human alpha1-antitrypsin promoter 5.  | Unknown | Unknown | Unknown |
| **LH2/Lim-1** | Unknown | Unknown | Unknown |
| **LR-1**Lr1 disease resistance protein 1.  | Unknown | Unknown | Unknown |
| **LSF**Also known as transcription factor CP2 (TFCP2) 1. TF that activates transcription of the α-globin gene; Regulates erythroid gene expression; Interacts with certain inflammatory response factors 1.  | Unknown | Unknown | • Potential interaction between the GARS-AIRS-GART Gene and LSF in Down syndrome-related AD [[124](#_ENREF_124)].• Polymorphism in LSF gene associated with AD and major depression [[125](#_ENREF_125)].• LSF gene polymorphism and risk of sporadic AD [[126](#_ENREF_126)]. |
| **LXRE-1**liver X receptor, nuclear receptor subfamily 1, group H, member 2 5.  | JNK 1/2 activation by TNF-α induces insulin resistance in human visceral adipocytes: reversal by liver X receptor (LXR) agonists [[127](#_ENREF_127)]. | Piperine, an LXRα antagonist, protects against hepatic steatosis and improves insulin signaling in mice fed a high-fat diet [[128](#_ENREF_128)]. | LXR activation attenuates inflammatory response and protects cholinergic neurons in APP/PS1 transgenic mice [[129](#_ENREF_129)]. |
| **LyF(1), LyF/IKAROS**Also known as IKZF1 IKAROS family zinc finger 1 (Ikaros) 1. TF family associated with chromatin remodeling; Regulator of lymphocyte differentiation. Several alternatively spliced transcript variants encoding different isoforms have been described for this gene 1. | Unknown | Ikaros regulates the human placental leucine aminopeptidase (P-LAP)/insulin-regulated aminopeptidase (IRAP) gene in choriocarcinoma trophoblastic cells, suggesting that Ikaros might be involved in placental development [[130](#_ENREF_130)].  | Novel susceptibility gene for AD [[131](#_ENREF_131)]. |
| **MBP-1**Myc-binding protein 1 [[132](#_ENREF_132)]. | Unknown  | Unknown | Unknown |
| **MDBP**Methylated DNA-Binding Protein 5.  | Unknown | Unknown | Unknown |
| **MEF-1**Myocyte enhancing factor 1 | Unknown | Unknown | Unknown |
| **MEF-2**Myocyte enhancing factor 2Regulate cellular differentiation and embryonic development; In adult organisms, MEF2 mediate the stress response in some tissues 3.  | Showed that JNK did not play a significant role in the activation of MEF2, rather p38 MAPK was identified [[133](#_ENREF_133), [134](#_ENREF_134" \o "Ornatsky, 1999 #547)]. | • MEF2 activation in skeletal muscle is regulated via parallel intracellular signaling pathways in response to insulin, cellular stress, or activation of AMPK [[135](#_ENREF_135)].• MEF2C activated by IGF-1 [[136](#_ENREF_136)]. | MEF2 mediates APP signaling pathways involved in the inhibition of neuron apoptosis; APP may mediate p38 MAPK-dependent phosphorylation and activation of MEF2; Once activated, MEF2 regulates neuronal survival [[137](#_ENREF_137)]. |
| **MEF-2a**Myocyte enhancing factor 2a | Unknown | Unknown | Variation at the MEF2A gene could be involved in the risk of late onset AD [[138](#_ENREF_138)]. |
| **MEF-3** | Unknown | MEF3 site controlled by IGF/PI3K/Akt pathway [[139](#_ENREF_139)]. | Unknown |
| **MRE**Metal Response Element 5.  | Unknown | MREs were identified in the promoter regions of the Ins1 and Ins2 genes [[140](#_ENREF_140)]. | Unknown |
| **msx-1/2/3**Msh homeobox 1/2/3; MSX-1 also known as HOX7; MSX-2 also known as HOX8 1.  | Unknown | Unknown  | Unknown |
| **MTF**MRE-binding transcription factor-1.Induces expression of metallothioneins; Nucleocytoplasmic shuttling protein that accumulates in the nucleus upon heavy metal exposure and binds to promoters containing a metal-responsive element (MRE) 1.  | • MTF-1 activation was inhibited by PKC, JNK, and PI3K inhibitors [[141](#_ENREF_141)].• Recombinant MTF-1 served as an *in vitro* substrate for casein kinase II, JNK and protein kinase C, but inhibition of these kinases *in vivo* did not significantly change the modification pattern of MTF-1 [[142](#_ENREF_142)]. | Mtf1 was shown to specifically bind to the MRE in the insulin gene and activate gene transcription [[140](#_ENREF_140)]. |  |
| **Myc-Max**Myc-associated factor X 1.Myc is an oncoprotein implicated in cell proliferation, differention and apoptosis 1. Max is the obligate heterodimerization partner of Myc [[143](#_ENREF_143)]. | Scaffolding protein, JLP, brings together Max and c-Myc along with JNK [[144](#_ENREF_144)]. | Insulin-induced stimulation of hepatic ODC mRNA expression is accompanied by a concomitant increase in the expression of c-myc and max mRNAs [[145](#_ENREF_145)]. | Unknown |
| **MyoG**Myogenic factor 4; Also known as myogenin 1. Muscle-specific TF that can induce myogenesis in a variety of cell types in tissue culture; Essential for the development of functional skeletal muscle 1.  | Inhibition of JNK resulted in IGF1 induced myogenin expression [[146](#_ENREF_146)]. | IGF1 can induce myogenin expression in myoblasts [[146](#_ENREF_146)]. | Unknown |
| **MyT1**Myelin transcription factor I 1. Binds to promoter regions of proteolipid proteins of the CNS and plays a role in the developing nervous system 1.  | JNK1 phosphorylates Myt1 to prevent UVA-induced skin cancer [[147](#_ENREF_147)]. | Male mice with pancreas-specific knockout of MyT1 showed attenuated glucose-induced insulin secretion in the adult islets [[148](#_ENREF_148)]. | May be the potential TF binding to major polymorphisms in the promoter region of cholesterol 24S-hydroxylase (CYP46A1) which were associated with AD [[149](#_ENREF_149)]. |
| **NCAM BP**Neural cell adhesion molecule 1. Member of the immunoglobulin superfamily; Involved in cell-to-cell interactions during development and differentiation; Involved in development of nervous system 1.  | JNK was not activated by NCAM [[150](#_ENREF_150)]. | Potential role of NCAM in promoting insulin signaling in adipocytes [[151](#_ENREF_151)]. | • Perturbation in polysialylation and/or NCAM expression in mouse models recapitulates many symptoms of human brain disorders such as schizophrenia, depression, anxiety and AD [[152](#_ENREF_152)].• Potential involvement of NCAM-expressing neurons in AD [[153](#_ENREF_153)]. |
| **NF-1, NF-1/L** (?)Neurofibromin 1 1. Functions as a negative regulator of the ras signal transduction pathway 1.  | Inhibition of NF-1X binding by c-Jun appears to play a role in regulating levels of human paplyomavirus JC activity [[154](#_ENREF_154)].  | • NFI proteins are important regulators of IGFBP5 expression in human osteoblasts [[155](#_ENREF_155)].• Upstream element from the human insulin receptor gene promoter contains binding sites for NF-1 [[156](#_ENREF_156)]. | Unknown |
| **NF-A3**Nuclear Factor A3 5.  | Unknown | Unknown | Unknown |
| **NF-Atx**Nuclear factor of activated T-cells; Expressed predominantly in the thymus 5.  | • Urosilic acid inhibited the activation of JNK and suppressed the activation of NFATx [[157](#_ENREF_157)].• EGCG induces IL-13 mRNA expression via the JNK-dependent NFATc1 pathway in KU812 cells [[158](#_ENREF_158)]. | Transcriptional control of IRS-2 gene expression is regulated by the NFAT pathway in islet β-cells [[159](#_ENREF_159)]. | Inhibition of astrocytic NFAT activity in primary cultures of neurons and glia dampened glutamate levels and alleviated neuronal death in response to pathogenic Aβ peptides [[160](#_ENREF_160)]. |
| **NF-E1/YY1**Involved in repressing and activating a diverse number of promoters; May direct histone deacetylases and acetyltransferases 1. NF-E1 is encoded by the same gene as the YY-1 protein. NF-E1 is also the human homologue to the mouse delta protein [[161](#_ENREF_161)]. | Unknown | Skeletal muscle-specific YY1 knockout mice were protected from rapamycin-induced diabetic-like symptoms potentially through the hyperactivation of insulin/IGF signaling [[162](#_ENREF_162)]. | • YY1 is an activator of BACE1 expression [[163](#_ENREF_163)].• Involvement of YY1 may be a novel mechanism in the development of AD [[164](#_ENREF_164)]. |
| **NF-E2**nuclear factor (erythroid-derived 2); Also known as p45 1.  | JNK phosphorylates p45/NF-E2 at Ser157 [[165](#_ENREF_165)]. | Unknown | Unknown |
| **NFE-6/CP1** Enhancer downstream of the human MLC1/3 locus; Target for multiple myogenic determination factors 5.  | Unknown | Unknown | unknown |
| **NF-Gma** | Unknown | Unknown | Unknown |
| **Nfil-2** | Unknown | Unknown | Unknown |
| **NFκB**Nuclear Factor Kappa BPolypeptide gene enhancer in B-cells 5.  | • Inflammatory cytokines stimulate the chemokines CCL2/MCP-1 and CCL7/MCP-3 through NFκB and MAPK dependent pathways in rat astrocytes [[166](#_ENREF_166)].• NADPH oxidase-related ROS-induced apoptosis is mediated via the JNK-dependent activation of NFκB in cardiomyocytes exposed to high glucose [[167](#_ENREF_167)]. | • There exists a link between the molecular actions of IKK/NFκB in neurons and Igf2 [[168](#_ENREF_168)].• NFκB was demonstrated to function as a crucial downstream effector of IGF-1R [[169](#_ENREF_169)]. | • Upregulation of APOE by Aβ in astroglial cells is mediated by an NFκB-element present in the 5'-flanking region of the APOE gene [[170](#_ENREF_170)].• NFκB triggers a repressive effect on Aβ production that contributes to maintaining its homeostasis [[171](#_ENREF_171)]. |
| **NF-Y**Nuclear transcription factor Y 1.  | • Suggest that drosophilla NF-Y is necessary for proper bsk gene expression and activity of JNK pathway during thorax development [[172](#_ENREF_172)].• JNK-bound promoters are enriched with binding motifs for NF-Y [[110](#_ENREF_110)]. | NF-Y site is required for full activation of the SREBP-1c promoter by insulin [[173](#_ENREF_173)]. | Unknown |
| **N-ras BP**N-ras promoter region 5.  | Unknown | Unknown | Unknown |
| **NZF-3**neural zinc finger factor 3; Also known as suppression of tumorigenicity 18 (St18) 1, and MyT3 [[148](#_ENREF_148)].  | Unknown | MyT1 inactivation in the developing pancreas could be masked by activation of its paralogs, Myt1L and MyT3 [[148](#_ENREF_148)]. | Unknown |
| **OCT**Oct family constitute the transcriptional network that maintains pluripotency in embryonic stem cells [[174](#_ENREF_174)].Oct-1, a TF involved in the oxidative stress pathway [[175](#_ENREF_175)]. | Unknown | Oct-1 as a transcriptional repressor of the carbohydrate response element binding protein ChREBP; Insulin stimulates ChREBP expression via attenuating the repressive effect of Oct-1 [[176](#_ENREF_176)]. | Unknown |
| **ODC**ornithine decarboxylase 5. Rate-limiting enzyme of the polyamine biosynthesis pathway 1.  | Unknown | Increased ODC activity and myoblast differentiation resulting from treatment with insulin [[177](#_ENREF_177)]. | Treatment of rat embryonic hippocampal neuronal cultures with Aβ increased ODC activity [[178](#_ENREF_178)]. |
| **ORE**osmotic response element 5.  | Unknown | Unknown | Unknown |
| **P-53**Tumor supressor | In Drosophila, the normally rapid JNK-dependent apoptotic response to genotoxic stress is significantly delayed in Dmp53 (Drosophila p53) mutants [[179](#_ENREF_179)].  | Unknown | Unknown |
| **PAX-1**Paired box 1 1. Members of the PAX family play critical roles during fetal development 1.  | Unknown | Unknown | unknown |
| **PAX-2**Paired box 2 1.  | Unknown | Has a role in the regulation of the insulin responsive element of the glucagon gene [[180](#_ENREF_180)]. | SNP identified in the pax-2 motif on the APP promoter [[181](#_ENREF_181)]. |
| **PAX-3**Paired box 3 1.  | Regulation of Wnt-signaling cascade entailing JNK activation is a function of Pax3 activity [[182](#_ENREF_182)]. | The fusion gene of PAX3/FKHR interacts with IGF2 to play a critical role in the oncogenesis of rhabdomyosarcoma [[183](#_ENREF_183), [184](#_ENREF_184)] | Unknown |
| **Pax-5**Paired box 5 1.B-cell lineage specific activator protein that is expressed at early, but not late stages of B-cell differentiation. May also play a role in neural development and spermatogenesis 1.  | Unknown | GH changed the expressions of TFs for B cell progenitors differentiation such as Pax-5, immunoglobulin-associated-alpha (Ig-alpha)/CD79a, Ig-beta/CD79b, and IGF-I [[185](#_ENREF_185)]. | Unknown |
| **PEBP-2**Also known as core binding factor beta (CBFB)  | Unknown | Unknown | Unknown |
| **Pit-1** Also known as POU class homeobox 1 (POU1F1) 1. Regulates genes involved in pituitary development and hormone expression 1.  | Unknown | Pit1 mutation results in a decreased activity of the insulin/IGF-1 pathway [[186](#_ENREF_186)]. | Unknown |
| **PO-B**DNA binding site of a transcription factor [[8](#_ENREF_8)]. | Unknown | Unknown | unknown |
| **PPAR**Peroxisome proliferative activated receptor 5. Belong to the steroid hormone receptor subfamily; Affect the expression of target genes involved in cell proliferation, cell differentiation and immune and inflammation responses 1.  | • Arginine decreased PPARγ transcriptional activity and the changes are due, in part, to phosphorylation of c-Jun [[186](#_ENREF_186)].• Activation of JNK signaling reduces fatty acid oxidation and prevents the PPARα down-regulation that occurs with LPS [[187](#_ENREF_187)]. | Activation of PPAR may help with improvements to insulin sensitivity in obese mice [[188](#_ENREF_188)]. | • PPAR activation helps facilitate amyloid clearance [[189](#_ENREF_189)].• Agonists for PPAR identified as neuroprotective [[190](#_ENREF_190)]. |
| **PPUR**purine-rich sequences binding sequence 5.  | Unknown | unknown | unknown |
| **PRDI-BFc**An inducible factor that binds to positive regulatory element of the human β-interferon gene 5. PRDI-BFc is interferon regulatory factor -2 (IRF-2), a known transcriptional repressor [[191](#_ENREF_191)].  | Unknown | Unknown | Unknown |
| **PTF1**Pancreas-specific transcription factor 5. Role in mammalian pancreatic development 1.  | Unknown | Postembryonic antagonism of Ptf1a induced the expression of insulin [[192](#_ENREF_192)]. | Unknown |
| **Pur-1**Also known as purine-rich element binding protein A (PURA) 1. Purine-binding transcription factor (MYC-associated zinc finger protein) 5.  | Unknown | Pur-1 can activate an insulin promoter in HeLa cells [[193](#_ENREF_193)]. | Unknown |
| **RB**Retinoblastoma tumor suppressor protein 5. Also known as pRb 1. Negative regulator of the cell cycle; Stabilizes constitutive heterochromatin; Active form binds E2F1 1.  | pRb suppresses camptothecin-induced apoptosis in human osteosarcoma Saos-2 cells by inhibiting JNK [[194](#_ENREF_194)]. | • RB and IDE interact within the proteosome and this may have growth regulatory consequences [[195](#_ENREF_195)].• Rb haploinsufficiency ameliorated insulin resistance [[196](#_ENREF_196)]. | • pRb/p107 is phosphorylated during Aβ treatment and the E2FxDP complex (downstream target) is required for Aβ-evoked neuronal death [[197](#_ENREF_197)].• Hyperphosphorylation of pRb associated with death of post mitotic neurons after injury [[198](#_ENREF_198)]. |
| **RFX**Regulatory factor X 1. RFX family of TFs are important in ciliogenesis control 1.  | JNK induces SHP1 expression through the binding of AP-4 and RFX-1 TFs to the epithelial tissue-specific SHP1 promoter [[199](#_ENREF_199)]. | RFX3 govern pancreatic endocrine cell differentiation - the presence of primary cilia on islet cells may play a key role in this process [[200](#_ENREF_200)]. | Unknown |
| **RIPE3a1**Rat insulin promoter element 3 5.  | Unknown | Unknown | Unknown |
| **RREB**Ras-responsive element binding protein 1 5. Involved in Ras/Raf-mediated cell differentiation 1.  | RREB is regulated by MAPKs and this may include JNK [[201](#_ENREF_201)]. | Unknown | Unknown |
| **SIF-1**sucrase-isomaltase (SI) 5.  | Unknown | Insulin suppressed disaccharidase activities and down-regulated SI complex [[202](#_ENREF_202)]/ | Unknown |
| **SMAD3/4** | TGF-β activates JNK which phosphorylates SMAD3 [[203](#_ENREF_203), [204](#_ENREF_204" \o "Yamagata, 2005 #611)]. | Insulin-like growth factor binding protein-3 (IGFBP-3) can stimulate Smad3 phosphorylation [[205](#_ENREF_205)]. | SMAD3/4 can induce APP expression [[206](#_ENREF_206)]. |
| **SP-1/ ASP**Ubiquitously expressed; Implicated in cell cycle regulation and chromatin remodeling 5. | Interleukin-18 induces EMMPRIN expression in primary cardiomyocytes via JNK/Sp1 signaling [[207](#_ENREF_207)]. | • Insulin increases zinc finger and BTB domain-containing 7A (Zbtb7A) expression through transcriptional regulation mediated by Sp1 in HepG2 cells [[208](#_ENREF_208)].• Sp1 is involved in the IGF-I-induced up-regulation of type II collagen [[209](#_ENREF_209)]. | SP1 can induce APP expression [[206](#_ENREF_206)]. |
| **SPERM-1** | Unknown | Unknown | Unknown |
| **SRE**Serum Response element. | JNK phosphorylates Elk-1 which dimerizes to form the SRF which binds the SRE [[210](#_ENREF_210)]. | • pTK81-SRE-Luc, a luciferase fusion gene that contains the SRE cloned 5' to a minimal thymidine kinase promoter and the luciferase gene: Treatment with IGF-I increased pTK81-SRE-Luc activity in a dose-dependent fashion [[211](#_ENREF_211)].• Insulin induces binding of the tertiary complex and a novel protein complex to the c-fos serum response element, mediated by SRE [[212](#_ENREF_212)]. | BDNF signaling results in the suppression of SRE-mediated transcription [[213](#_ENREF_213)]. |
| **SRF**Serum Response Factor. | JNK phosphorylates Elk-1 which dimerizes to form the SRF which binds the SRE [[213](#_ENREF_213)]. | • SRF is important for IGF-1-induced osteoblast differentiation [[214](#_ENREF_214)]• SRF is a glucose concentration-sensitive regulator of insulin gene expression [[215](#_ENREF_215)]. | Silencing SRF normalized contractile protein content and reversed a hypercontractile phenotype in AD VSMC [[216](#_ENREF_216)]. |
| **SRY**Sex determining region Y 5.Initiates male sex determination 1.  | Unknown | Embryos lacking functional insulin/IGF signaling exhibit a delay of SRY upregulation [[217](#_ENREF_217)].  | Unknown |
| **STAT-1**Signal transducer and activator of transcription 1 1. Mediates expression of a variety of genes thought to be important cell viability in response to different cell stimuli and pathogens 1.  | Induction of PLSCR1 transcription through STAT1 depends upon sequential activation of PKCδ and JNK [[218](#_ENREF_218)]. | IFNγ attenuates insulin sensitivity and suppresses differentiation in human adipocytes, an effect most likely mediated via sustained JAK-STAT1 pathway activation [[219](#_ENREF_219)]. | • IFN-γ activates STAT1 which modulates BACE1 protein expression in astrocytes [[220](#_ENREF_220)].• STAT1α in cell nuclei may be involved in inflammatory activation in AD brains [[221](#_ENREF_221)]. |
| **STAT-3**Signal transducer and activator of transcription 3 1. Activated in response to various cytokines and growth factors including IFNs, EGF, IL5, IL6, HGF, LIF and BMP2; Plays a key role in many cellular processes such as cell growth and apoptosis 1.  | • Following the binding of cytokines to their cognate receptor, STATs are activated by members of the JAK family of tyrosine kinases 4. • Inhibition of JAK2/STAT3 induced apoptosis via the mitochondrial apoptotic pathway [[222](#_ENREF_222)]. | • STAT3 activation is highly dependent on GSK3.[[223](#_ENREF_223)].• Excessive STAT3 signaling in the development of skeletal muscle insulin resistance in T2D [[224](#_ENREF_224)]. | • Aβ induces hepatic insulin resistance *in vivo* via JAK2, suggesting that inhibition of Aβ signaling is a new strategy toward resolving insulin resistance and T2DM [[225](#_ENREF_225)].• Involvement of STAT3 in mediating Aβ-induced neuronal death [[226](#_ENREF_226)].  |
| **STAT-4**Signal transducer and activator of transcription 4 1. Essential for mediating responses to IL-12 in lymphocytes and regulating the differentiation of T helper cells 1.  | Unknown | Selective inhibition of the STAT4 signal transduction pathway might constitute a novel and attractive approach to prevent clinical insulin-dependent DM in prediabetic individuals at risk [[227](#_ENREF_227)]. | Unknown |
| **STAT-5b**Signal transducer and activator of transcription 5b 5. Mediates signal transduction triggered by IL-2, IL-4, CSF1; Involved in apoptosis and adult mammary gland development 1.  | Unknown | Multiple Stat5b-binding response elements are responsible for highly regulated control of IGF-I gene activity by GH [[228](#_ENREF_228)]. | Unknown |
| **STAT-6**Signal transducer and activator of transcription 6 1.Exerts IL4 mediated biological responses; Induces the expression of BCL2L1/BCL-X(L), which is responsible for the anti-apoptotic activity of IL4 1.  | • Inactivation of STAT6 by JNK-dependent Ser-707 phosphorylation may be one mechanism of controlling the balance between IL-1β and IL-4 signals [[229](#_ENREF_229)].• STAT6 phosphorylation/activation induced by IL-13 is mediated by activation of JAK1 [[230](#_ENREF_230)]. | • Disruption of STAT6 decreases insulin action and enhances a PPARα driven program of oxidative metabolism [[231](#_ENREF_231)]. • IL-4 receptors are functionally competent in pancreatic β-cells and they signal via PI3K and JAK/STAT pathways [[232](#_ENREF_232)]. | Unknown |
| **T3R**thyroid hormone receptor; Also known as c-erbA 5.  | Unknown | Insulin/IGF-I reduce levels of c-erbA α 1 and α 2 mRNA [[233](#_ENREF_233)]. | Unknown |
| **Tax/CREB**cAMP responsive element binding protein 1. TAX also known as contactin 2 (CNTN2) and TAG-1 1. | JNK-1 is required for Tax-induced proliferation of Jurkat leukemia cells [[234](#_ENREF_234)]. | Retinol binding protein 4 (RBP4) is essential in insulin resistance; CREB identified as target TF involved in RBP4-mediated upregulation of PGC-1β transcription [[235](#_ENREF_235)]. | • Recent studies have demonstrated the importance of the CREB pathway to the process of learning and memory [[236](#_ENREF_236)].• TAG-1 identified as a natural ligand of APP [[237](#_ENREF_237)]. |
| **TCE**Transforming Growth Factor 1 control element 5. | Unknown | Unknown | Unknown |
| **TCF/LEF**T cell factor/lymphocyte enhancer binding factor 5.TCF also known as hepatocyte nuclear factor 4 (HNF4) 1.  | Tcf4 decreases expression of c-Myc and MAP4K1, JNK activation, and AP-1 dependent transcription [[63](#_ENREF_63)]. | IGF-I stimulation of C2C12 myotubes increases mouse type IIb MyHC promoter activity, likely through signaling of PI3K, GSK-3β, β-catenin, and a Tcf/Lef binding site [[238](#_ENREF_238)]. | Presenilin 1 negatively regulates β-catenin/TCF/LEF signaling independently of APP and notch processing [[239](#_ENREF_239)]. |
| **TFE3**Transcription factor binding to IGHM enhancer 3 1.  | Unknown | • TFE3 regulates muscle metabolic gene expression, increases glycogen stores, and enhances insulin sensitivity in mice [[240](#_ENREF_240)]• TFE3 transcriptionally activates hepatic IRS-2, participates in insulin signaling and ameliorates diabetes [[241](#_ENREF_241)]. | Unknown |
| **TGT-3**TTF-1 (Thyroid Transcription Factor 1) binding element 5.  | Unknown | • Increased expression of TTF-1 and T1α in lung specimens cultured in the presence of IGF-2 [[242](#_ENREF_242)].• TTF-1 gene expression is interdependently regulated by TSH and serum growth factors including insulin [[243](#_ENREF_243)]. | Unknown |
| **TIF-1**Also known as tripartite motif containing 24 (TRIM24) 1. Mediates transcriptional control by interaction with the activation function 2 (AF2) region of several nuclear receptors including estrogen, retinoic and vitamin D3 receptors 1.  | TIF-IA is a major target of the JNK2 signaling pathway [[244](#_ENREF_244)]. | Unknown | Unknown |
| **TREF1/2**Transferrin receptor (TR) binding protein 5. | Unknown | Unknown | Unknown |
| **USF-1**Upstream transcription factor 5. | Unknown | Single-nucleotide polymorphism rs2073658 prevents the inductive effect of insulin on the expression of USF1 in muscle and fat [[245](#_ENREF_245)]. | USF can bind the promoter for APP [[246](#_ENREF_246)]. |
| **v-Maf**v-maf musculoaponeurotic fibrosarcoma oncogene homolog 5.Regulates lens fiber cell development, T-cell apoptosis and chondrocyte terminal differentiation 1.  | Activated PPARδ can inhibit the activation of JNK and increase the expression of MafA [[247](#_ENREF_247)]. | Likely that the augmented expression of c-Jun in diabetic islets decreases MafA expression and thereby reduces insulin biosynthesis, often observed in type 2 diabetes [[248](#_ENREF_248)] | Unknown |
| **WT1**Wilms tumor 1 5.Essential role in the development of the urogenital system 1. | LPS-stimulated WT1 interacting protein nuclear translocation required JNK activity [[249](#_ENREF_249)]. | Wt1 gene is a target of IGF-1 in neurally derived cells [[250](#_ENREF_250)]. | May play a role in the neurodegeneration observed in AD [[251](#_ENREF_251)]. |
| **X2 BP**X2 binding protein A CREB/ATF family transcription factor binds as a homodimer [[7](#_ENREF_7)]. | Unknown | Unknown | Unknown |
| **XBP1**X-box binding protein 1; Also known as TREB-5; hXBP-1 1. | Unknown | Treatment of non-obese diabetic mice with insulin activated hepatic XBP1 [[252](#_ENREF_252)]. | XBP1 shows neuroprotective activity in two different AD models, flies expressing Aβ and mammalian cultured neurons treated with Aβ oligomers [[253](#_ENREF_253)]. |
| **ZNF174**Zinc-finger protein 174 5. | Unknown | Unknown | Unknown |

1. From http://www.ncbi.nlm.nih.gov/gene/
2. From http://www.uniprot.org/
3. From http://en.wikipedia.org
4. From http://www.ncbi.nlm.nih.gov/biosystems/
5. From http://www.panomics.com/

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