# Functional Module Pathway Analysis Report

# Research Task Description

As a molecular biology researcher, you are required to complete the following analysis task based on the provided biological information using your professional expertise and literature search capabilities. Please do not use any large language models or AI tools, but rely on your professional background and literature research to complete this work.

## Research Objectives

1. Identify the core biological process that describes this module based on the provided pathway information.

2. Analyze functional relationships among genes/proteins, focusing on: shared signaling pathways or molecular mechanisms, synergistic or antagonistic interactions, disease relevance and clinical significance.

3. Avoid isolated functional descriptions: Instead of simply listing individual gene/protein functions, group genes/proteins with similar functions and analyze their collective mechanisms of action.

4. Name the module: Provide a concise and accurate name for this functional module, ensuring it highlights key biological processes, disease associations, or molecular mechanisms while avoiding overly generic terms.

5. Assess confidence score (0.00 - 1.00): This score reflects the degree of overlap or convergence of input genes/proteins and pathways on a single, coherent biological process.

6. Integrate research insights: Ensure that the generated summary reflects findings from your literature research.

## Suggested Research Methods

• Literature Search: Use databases such as PubMed, Web of Science for relevant literature

• Pathway Databases: Consult KEGG, Reactome, GO databases to validate pathway information

• Protein Interaction Databases: Use STRING, BioGRID to understand molecular interactions

• Disease Databases: Query OMIM, DisGeNET to understand disease associations

## Final Output Requirements

Please provide your analysis results strictly in JSON format:

{
"module\_name": "Your concise module name here",
"summary": "A detailed, literature-integrated explanation of the module's function, key genes/proteins, and relevant biological processes.",
"confidence\_score": "A value between 0.00 and 1.00"
}

Note: Please rely entirely on your professional knowledge, literature search, and critical analysis to complete this task. Do not use any AI-assisted tools.

# Module Analysis Data

## Module 1

Pathway 1: hsa04210 (KEGG) Apoptosis

Apoptosis is a genetically programmed process for the elimination of damaged or redundant cells by activation of caspases (aspartate-specific cysteine proteases). The onset of apoptosis is controlled by numerous interrelating processes. The 'extrinsic' pathway involves stimulation of members of the tumor necrosis factor (TNF) receptor subfamily, such as TNFRI, CD95/Fas or TRAILR (death receptors), located at the cell surface, by their specific ligands, such as TNF-alpha, FasL or TRAIL, respectively. The 'intrinsic' pathway is activated mainly by non-receptor stimuli, such as DNA damage, ER stress, metabolic stress, UV radiation or growth-factor deprivation. The central event in the 'intrinsic' pathway is the mitochondrial outer membrane permeabilization (MOMP), which leads to the release of cytochrome c. These two pathways converge at the level of effector caspases, such as caspase-3 and caspase-7. The third major pathway is initiated by the constituents of cytotoxic granules (e.g. Perforin and Granzyme B) that are released by CTLs (cytotoxic T-cells) and NK (natural killer) cells. Granzyme B, similarly to the caspases, cleaves its substrates after aspartic acid residues, suggesting that this protease has the ability to activate members of the caspase family directly. It is the balance between the pro-apoptotic and anti-apoptotic signals that eventually determines whether cells will undergo apoptosis, survive or proliferate. TNF family of ligands activates anti-apoptotic or cell-survival signals as well as apoptotic signals. NGF and Interleukin-3 promotes the survival, proliferation and differentiation of neurons or hematopoietic cells, respectively. Withdrawal of these growth factors leads to cell death, as described above.

Pathway 2: GO:0000165 (GO) MAPK cascade

An intracellular protein kinase cascade containing at least a MAP kinase (MAPK). It starts with the activation of a MAP3K, and the consecutive activation of a MPK2K and a MAPK. The cascade can also contain an additional tier: the upstream MAP4K. The kinases in each tier phosphorylate and activate the kinase in the downstream tier to transmit a signal within a cell.

Pathway 3: GO:0004672 (GO) protein kinase activity

Catalysis of the phosphorylation of an amino acid residue in a protein, usually according to the reaction: a protein + ATP = a phosphoprotein + ADP.

Pathway 4: GO:0004674 (GO) protein serine/threonine kinase activity

Catalysis of the reactions: ATP + protein serine = ADP + protein serine phosphate, and ATP + protein threonine = ADP + protein threonine phosphate.

Pathway 5: GO:0004707 (GO) MAP kinase activity

Catalysis of the reaction: protein + ATP = protein phosphate + ADP. This reaction is the phosphorylation of proteins. Mitogen-activated protein kinase; a family of protein kinases that perform a crucial step in relaying signals from the plasma membrane to the nucleus. They are activated by a wide range of proliferation- or differentiation-inducing signals; activation is strong with agonists such as polypeptide growth factors and tumor-promoting phorbol esters, but weak (in most cell backgrounds) by stress stimuli.

Pathway 6: GO:0070371 (GO) ERK1 and ERK2 cascade

A MAPK cascade containing at least the ERK1 or ERK2 MAP kinases. It starts with the activation of a MAP3K, and the consecutive activation of a MPK2K and of ERK1 or ERK2. The cascade can also contain an additional tier: the upstream MAP4K. The kinases in each tier phosphorylate and activate the kinase in the downstream tier. The ERK1/ERK2 cascade is activated by mitogens, growth factors, G protein-coupled receptors, and results in cellular responses such as cell proliferation, cell differentiation and development.

Pathway 7: hsa04010 (KEGG) MAPK signaling pathway

The mitogen-activated protein kinase (MAPK) cascade is a highly conserved module that is involved in various cellular functions, including cell proliferation, differentiation and migration. Mammals express at least four distinctly regulated groups of MAPKs, extracellular signal-related kinases (ERK)-1/2, Jun amino-terminal kinases (JNK1/2/3), p38 proteins (p38alpha/beta/gamma/delta) and ERK5, that are activated by specific MAPKKs: MEK1/2 for ERK1/2, MKK3/6 for the p38, MKK4/7 (JNKK1/2) for the JNKs, and MEK5 for ERK5. Each MAPKK, however, can be activated by more than one MAPKKK, increasing the complexity and diversity of MAPK signalling. Presumably each MAPKKK confers responsiveness to distinct stimuli. For example, activation of ERK1/2 by growth factors depends on the MAPKKK c-Raf, but other MAPKKKs may activate ERK1/2 in response to pro-inflammatory stimuli.

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## Module 2

Pathway 1: GO:0051147 (GO) regulation of muscle cell differentiation

Any process that modulates the frequency, rate or extent of muscle cell differentiation.

Pathway 2: GO:0051146 (GO) striated muscle cell differentiation

The process in which a relatively unspecialized cell acquires specialized features of a striated muscle cell; striated muscle fibers are divided by transverse bands into striations, and cardiac and voluntary muscle are types of striated muscle.

Pathway 3: GO:0051148 (GO) negative regulation of muscle cell differentiation

Any process that stops, prevents, or reduces the frequency, rate or extent of muscle cell differentiation.

Pathway 4: GO:0051153 (GO) regulation of striated muscle cell differentiation

Any process that modulates the frequency, rate or extent of striated muscle cell differentiation.

Pathway 5: GO:0051154 (GO) negative regulation of striated muscle cell differentiation

Any process that stops, prevents, or reduces the frequency, rate or extent of striated muscle cell differentiation.

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## Module 3

Pathway 1: R-HSA-8852135 (Reactome) Protein ubiquitination

Ubiquitin is a small, 76 amino acid residue protein that is conjugated by E3 ubiquitin ligases to other proteins in order to regulate their function or degradation (enzymatic cascade reviewed in Neutzner and Neutzner 2012, Kleiger and Mayor 2014, structures and mechanisms of conjugating enzymes reviewed in Lorenz et al. 2013). Ubiquitination of target proteins usually occurs between the C-terminal glycine residue of ubiquitin and a lysine residue of the target, although linkages with cysteine, serine, and threonine residues are also observed (reviewed in Wang et al. 2012, McDowell and Philpott 2013).
Ubiquitin must first be processed from larger precursors and then activated by formation of a thiol ester bond between ubiquitin and an E1 activating enzyme (UBA1 or UBA6) and transfer to an E2 conjugating enzyme before being transferred by an E3 ligase to a target protein. Precursor proteins containing multiple ubiquitin monomers (polyubiquitins) are produced from the UBB and UBC genes; precursors containing a single ubiquitin monomer and a ribosomal protein are produced from the UBA52 and RPS27A genes. Many proteases (deubiquitinases) may potentially process these precursors yielding monomeric ubiquitin. The proteases OTULIN and USP5 are particularly active in cleaving the polyubiquitin precursors, whereas the proteases UCHL3, USP7, and USP9X cleave the ubiquitin-ribosomal protein precursors yielding ubiquitin monomers (Grou et al. 2015). A resultant ubiquitin monomer is activated by adenylation of the C-terminal glycine followed by conjugation of the C-terminus to a cysteine residue of the E1 enzymes UBA1 or UBA6 via a thiol ester bond. The ubiquitin is then transferred from the E1 enzyme to a cysteine residue of one of several E2 enzymes (reviewed in van Wijk and Timmers 2010, Stewart et al. 2016). Through a less well characterized mechanism, E3 ubiquitin ligases then bring a target protein and the E2-ubiquitin conjugate into proximity so that the ubiquitin is transferred via formation of an amide bond to a particular lysine residue (or, in rarer cases, a thiol ester bond to a cysteine residue or an ester bond to a serine or threonine residue) of the target protein (reviewed in Berndsen and Wolberger 2014). Based on protein homologies, families of E3 ubiquitin ligases have been identified that include RING-type ligases (reviewed in Deshaies et al. 2009, Metzger et al. 2012, Metzger et al. 2014), HECT-type ligases (reviewed in Rotin et al. 2009, Metzger et al. 2012), and RBR-type ligases (reviewed in Dove et al. 2016). A subset of the RING-type ligases participate in CULLIN-RING ligase complexes (CRLs which include SCF complexes, reviewed in Lee and Zhou 2007, Genschik et al. 2013, Skaar et al. 2013, Lee et al. 2014).
Some E3-E2 combinations catalyze mono-ubiquitination of the target protein (reviewed in Nakagawa and Nakayama 2015). Other E3-E2 combinations catalyze conjugation of further ubiquitin monomers to the initial ubiquitin, forming polyubiquitin chains. (It may also be possible for some E3-E2 combinations to preassemble polyubiquitin and transfer it as a unit to the target protein.) Ubiquitin contains several lysine (K) residues and a free alpha amino group to which further ubiquitin can be conjugated. Thus different types of polyubiquitin are possible: K11 linked polyubiquitin is observed in endoplasmic reticulum-associated degradation (ERAD), K29 linked polyubiquitin is observed in lysosomal degradation, K48 linked polyubiquitin directs target proteins to the proteasome for degradation, whereas K63 linked polyubiquitin generally acts as a scaffold to recruit other proteins in several cellular processes, notably DNA repair (reviewed in Komander et al. 2009). Ubiquitination is highly regulated (reviewed in Vittal et al. 2015) and affects all cellular processes including DNA damage response (reviewed in Brown and Jackson 2015), immune signaling (reviewed in Park et al. 2014, Lutz-Nicoladoni et al. 2015), and regulation of normal and cancerous cell growth (reviewed in Skaar and Pagano 2009, Yerlikaya and Yontem 2013, Strikoudis et al. 2014).

Pathway 2: hsa04120 (KEGG) Ubiquitin mediated proteolysis

Protein ubiquitination plays an important role in eukaryotic cellular processes. It mainly functions as a signal for 26S proteasome dependent protein degradation. The addition of ubiquitin to proteins being degraded is performed by a reaction cascade consisting of three enzymes, named E1 (ubiquitin activating enzyme), E2 (ubiquitin conjugating enzyme), and E3 (ubiquitin ligase). Each E3 has specificity to its substrate, or proteins to be targeted by ubiquitination. Many E3s are discovered in eukaryotes and they are classified into four types: HECT type, U-box type, single RING-finger type, and multi-subunit RING-finger type. Multi-subunit RING-finger E3s are exemplified by cullin-Rbx E3s and APC/C. They consist of a RING-finger-containing subunit (RBX1 or RBX2) that functions to bind E2s, a scaffold-like cullin molecule, adaptor proteins, and a target recognizing subunit that binds substrates.

Pathway 3: hsa03050 (KEGG) Proteasome

The proteasome is a protein-destroying apparatus involved in many essential cellular functions, such as regulation of cell cycle, cell differentiation, signal transduction pathways, antigen processing for appropriate immune responses, stress signaling, inflammatory responses, and apoptosis. It is capable of degrading a variety of cellular proteins in a rapid and timely fashion and most substrate proteins are modified by ubiquitin before their degradation by the proteasome. The proteasome is a large protein complex consisting of a proteolytic core called the 20S particle and ancillary factors that regulate its activity in various ways. The most common form is the 26S proteasome containing one 20S core particle and two 19S regulatory particles that enable the proteasome to degrade ubiquitinated proteins by an ATP-dependent mechanism. Another form is the immunoproteasome containing two 11S regulatory particles, PA28 alpha and PA28 beta, which are induced by interferon gamma under the conditions of intensified immune response. Other regulatory particles include PA28 gamma and PA200. Although PA28 gamma also belongs to a family of activators of the 20S proteasome, it is localized within the nucleus and forms a homoheptamer. PA28 gamma has been implicated in the regulation of cell cycle progression and apoptosis. PA200 has been identified as a large nuclear protein that stimulates proteasomal hydrolysis of peptides.

Pathway 4: GO:0016567 (GO) protein ubiquitination

The process in which one or more ubiquitin groups are added to a protein.

Pathway 5: GO:0061630 (GO) ubiquitin protein ligase activity

Catalysis of the transfer of ubiquitin to a substrate protein via the reaction X-ubiquitin + S = X + S-ubiquitin, where X is either an E2 or E3 enzyme, the X-ubiquitin linkage is a thioester bond, and the S-ubiquitin linkage is an amide bond: an isopeptide bond between the C-terminal glycine of ubiquitin and the epsilon-amino group of lysine residues in the substrate or, in the linear extension of ubiquitin chains, a peptide bond the between the C-terminal glycine and N-terminal methionine of ubiquitin residues.

Expected JSON Output Format:

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## Module 4

Pathway 1: GO:0098978 (GO) glutamatergic synapse

A synapse that uses glutamate as a neurotransmitter.

Pathway 2: GO:0098985 (GO) asymmetric, glutamatergic, excitatory synapse

A neuron to neuron synapse with a postsynaptic density, that uses glutamate as a neurotransmitter and whose activity results in excitatory postsynaptic potentials.

Pathway 3: hsa04724 (KEGG) Glutamatergic synapse

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system(CNS). Glutamate is packaged into synaptic vesicles in the presynaptic terminal. Once released into the synaptic cleft, glutamate acts on postsynaptic ionotropic glutamate receptors (iGluRs) to mediate fast excitatory synaptic transmission. Glutamate can also act on metabotropic glutamate receptors (mGluRs) and exert a variety of modulatory effects through their coupling to G proteins and the subsequent recruitment of second messenger systems. Presynaptically localized Group II and Group III mGluRs are thought to represent the classical inhibitory autoreceptor mechanism that suppresses excess glutamate release. After its action on these receptors, glutamate can be removed from the synaptic cleft by EAATs located either on the presynaptic terminal, neighboring glial cells, or the postsynaptic neuron. In glia, glutamate is converted to glutamine, which is then transported back to the presynaptic terminal and converted back to glutamate.

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## Module 5

Pathway 1: hsa03030 (KEGG) DNA replication

A complex network of interacting proteins and enzymes is required for DNA replication. Generally, DNA replication follows a multistep enzymatic pathway. At the DNA replication fork, a DNA helicase (DnaB or MCM complex) precedes the DNA synthetic machinery and unwinds the duplex parental DNA in cooperation with the SSB or RPA. On the leading strand, replication occurs continuously in a 5 to 3 direction, whereas on the lagging strand, DNA replication occurs discontinuously by synthesis and joining of short Okazaki fragments. In prokaryotes, the leading strand replication apparatus consists of a DNA polymerase (pol III core), a sliding clamp (beta), and a clamp loader (gamma delta complex). The DNA primase (DnaG) is needed to form RNA primers. Normally, during replication of the lagging-strand DNA template, an RNA primer is removed either by an RNase H or by the 5 to 3 exonuclease activity of DNA pol I, and the DNA ligase joins the Okazaki fragments. In eukaryotes, three DNA polymerases (alpha, delta, and epsilon) have been identified. DNA primase forms a permanent complex with DNA polymerase alpha. PCNA and RFC function as a clamp and a clamp loader. FEN 1 and RNase H1 remove the RNA from the Okazaki fragments and DNA ligase I joins the DNA.

Pathway 2: R-HSA-68952 (Reactome) DNA replication initiation

DNA polymerases are not capable of de novo DNA synthesis and require synthesis of a primer, usually by a DNA-dependent RNA polymerase (primase) to begin DNA synthesis. In eukaryotic cells, the primer is synthesized by DNA polymerase alpha:primase. First, the DNA primase portion of this complex synthesizes approximately 6-10 nucleotides of RNA primer and then the DNA polymerase portion synthesizes an additional 20 nucleotides of DNA (Frick & Richardson 2002; Wang et al 1984).

Pathway 3: R-HSA-69306 (Reactome) DNA Replication

Studies in the past decade have suggested that the basic mechanism of DNA replication initiation is conserved in all kingdoms of life. Initiation in unicellular eukaryotes, in particular Saccharomyces cerevisiae (budding yeast), is well understood, and has served as a model for studies of DNA replication initiation in multicellular eukaryotes, including humans. In general terms, the first step of initiation is the binding of the replication initiator to the origin of replication. The replicative helicase is then assembled onto the origin, usually by a helicase assembly factor. Either shortly before or shortly after helicase assembly, some local unwinding of the origin of replication occurs in a region rich in adenine and thymine bases (often termed a DNA unwinding element, DUE). The unwound region provides the substrate for primer synthesis and initiation of DNA replication. The best-defined eukaryotic origins are those of S. cerevisiae, which have well-conserved sequence elements for initiator binding, DNA unwinding and binding of accessory proteins. In multicellular eukaryotes, unlike S. cerevisiae, these loci appear not to be defined by the presence of a DNA sequence motif. Indeed, choice of replication origins in a multicellular eukaryote may vary with developmental stage and tissue type. In cell-free models of metazoan DNA replication, such as the one provided by Xenopus egg extracts, there are only limited DNA sequence specificity requirements for replication initiation (Kelly & Brown 2000; Bell & Dutta 2002; Marahrens & Stillman 1992; Cimbora & Groudine 2001; Mahbubani et al 1992, Hyrien & Mechali 1993).

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## Module 6

Pathway 1: GO:0009055 (GO) electron transfer activity

A molecular function representing the directed movement of electrons from one molecular entity to another, typically mediated by electron carriers or acceptors, resulting in the transfer of energy and/or the reduction-oxidation (redox) transformation of chemical species. This activity is fundamental to various biological processes, including cellular respiration and photosynthesis, as well as numerous enzymatic reactions involved in metabolic pathways.

Pathway 2: GO:0045251 (GO) electron transfer flavoprotein complex

A protein complex facilitating the electron transfer from an acyl-CoA molecule to ubiquinone via its flavin adenine dinucleotide (FAD) cofactor. Usually contains an alpha and a beta subunit and the structural cofactor adenosine monophosphate (AMP). Part of a system that oxidizes an acyl-CoA molecule and reduces ubiquinone and other acceptors in the electron transport system.

Pathway 3: hsa00190 (KEGG) Oxidative phosphorylation

NA

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}

## Module 7

Pathway 1: GO:0002250 (GO) adaptive immune response

An immune response mediated by cells expressing specific receptors for antigens produced through a somatic diversification process, and allowing for an enhanced secondary response to subsequent exposures to the same antigen (immunological memory).

Pathway 2: GO:0006955 (GO) immune response

Any immune system process that functions in the calibrated response of an organism to a potential internal or invasive threat.

Pathway 3: hsa04660 (KEGG) T cell receptor signaling pathway

Activation of T lymphocytes is a key event for an efficient response of the immune system. It requires the involvement of the T-cell receptor (TCR) as well as costimulatory molecules such as CD28. Engagement of these receptors through the interaction with a foreign antigen associated with major histocompatibility complex molecules and CD28 counter-receptors B7.1/B7.2, respectively, results in a series of signaling cascades. These cascades comprise an array of protein-tyrosine kinases, phosphatases, GTP-binding proteins and adaptor proteins that regulate generic and specialised functions, leading to T-cell proliferation, cytokine production and differentiation into effector cells.

Pathway 4: hsa04662 (KEGG) B cell receptor signaling pathway

B cells are an important component of adaptive immunity. They produce and secrete millions of different antibody molecules, each of which recognizes a different (foreign) antigen. The B cell receptor (BCR) is an integral membrane protein complex that is composed of two immunoglobulin (Ig) heavy chains, two Ig light chains and two heterodimers of Ig-alpha and Ig-beta. After BCR ligation by antigen, three main protein tyrosine kinases (PTKs) -the SRC-family kinase LYN, SYK and the TEC-family kinase BTK- are activated. Phosphatidylinositol 3-kinase (PI3K) and phospholipase C-gamma 2 (PLC-gamma 2) are important downstream effectors of BCR signalling. This signalling ultimately results in the expression of immediate early genes that further activate the expression of other genes involved in B cell proliferation, differentiation and Ig production as well as other processes.

Pathway 5: R-HSA-1280218 (Reactome) Adaptive Immune System

Adaptive immunity refers to antigen-specific immune response efficiently involved in clearing the pathogens. The adaptive immune system is comprised of B and T lymphocytes that express receptors with remarkable diversity tailored to recognize aspects of particular pathogens or antigens. During infection, dendritic cells (DC) which act as sentinels in the peripheral tissues recognize and pick up the pathogen in the form of antigenic determinants and then process these antigens and present them to T cells. These T cells of appropriate specificity respond to the antigen, and either kill the pathogen directly or secrete cytokines that will stimulate B lymphocyte response. B cells provide humoral immunity by secreting antibodies specific for the pathogen or antigen.

Pathway 6: R-HSA-388841 (Reactome) Regulation of T cell activation by CD28 family

Optimal activation of T lymphocytes requires a carefully orchestrated interplay between two key signals. The first signal originates from the T cell receptor (TCR) recognizing a specific antigen. However, this initial encounter is insufficient on its own. A crucial "costimulatory" signal is needed for full T cell activation, delivered by the engagement of costimulatory receptors, such as CD28, on the T cell surface with their corresponding ligands on antigen-presenting cells (APCs) (Chen & Flies 2013, Acuto et al. 2003, Slavik et al. 1999).
The CD28 superfamily is central to costimulation, encompassing a diverse group of receptors including CD28, CTLA-4, ICOS, PD-1, and BTLA. These receptors have both positive and negative influences on T cell activation. CD28 and ICOS provide a positive boost, while CTLA-4, PD-1, and BTLA act as inhibitory brakes. CD28 and CTLA-4 bind to B7 family ligands CD80 (B7.1) and CD86 (B7.2), with CD28 delivering stimulatory signals and CTLA-4 providing inhibitory signals. ICOS interacts with ICOS ligand (ICOS-L), enhancing T cell activation and function. PD-1 binds to PD-L1 and PD-L2, mediating inhibitory signals that modulate the immune response. BTLA engages with HVEM (Herpesvirus entry mediator), transmitting inhibitory signals. This balance between stimulatory and inhibitory signals is essential, allowing the immune system to mount effective responses against pathogens while preventing the induction of T cell unresponsiveness and apoptosis (Chen & Flies 2013, Sharpe & Freeman 2002, Carreno & Collins 2002).
The expression of these receptors varies: CD28 is constantly present on naive T cells, whereas CTLA-4 expression depends on prior CD28 engagement. ICOS, PD-1, and BTLA are induced only after initial T cell stimulation. These variations in expression ensure precise regulation of T cell responses at different stages of activation (Sharpe & Freeman 2002). The receptors themselves also exhibit structural differences. CD28, CTLA-4, and ICOS share a single extracellular domain resembling an immunoglobulin molecule (IgV-like). In contrast, BTLA has a distinct structure with an IgC-like domain. Similarly, the costimulatory ligands, such as B7-1 and B7-2, have unique structural features that enable specific interactions with their partner receptors

Pathway 7: R-HSA-983705 (Reactome) Signaling by the B Cell Receptor (BCR)

Mature B cells express IgM and IgD immunoglobulins which are complexed at the plasma membrane with Ig-alpha (CD79A, MB-1) and Ig-beta (CD79B, B29) to form the B cell receptor (BCR) (Fu et al. 1974, Fu et al. 1975, Kunkel et al. 1975, Van Noesel et al. 1992, Sanchez et al. 1993, reviewed in Brezski and Monroe 2008). Binding of antigen to the immunoglobulin activates phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic tails of Ig-alpha and Ig-beta by Src family tyrosine kinases, including LYN, FYN, and BLK (Nel et al. 1984, Yamanashi et al. 1991, Flaswinkel and Reth 1994, Saouaf et al. 1994, Hata et al. 1994, Saouaf et al. 1995, reviewed in Gauld and Cambier 2004, reviewed in Harwood and Batista 2010).
The protein kinase SYK binds the phosphorylated immunoreceptor tyrosine-activated motifs (ITAMs) on the cytoplasmic tails of Ig-alpha (CD79A, MB-1) and Ig-beta (CD79B, B29) (Wienands et al. 1995, Rowley et al. 1995, Tsang et al. 2008). The binding causes the activation and autophosphorylation of SYK (Law et al. 1994, Baldock et al. 2000, Irish et al. 2006, Tsang et al. 2008, reviewed in Bradshaw 2010).
Activated SYK and other kinases phosphorylate BLNK (SLP-65), BCAP, and CD19 which serve as scaffolds for the assembly of large complexes, the signalosomes, by recruiting phosphoinositol 3-kinase (PI3K), phospholipase C gamma (predominantly PLC-gamma2 in B cells, Coggeshall et al. 1992), NCK, BAM32, BTK, VAV1, and SHC. The effectors are phosphorylated by SYK and other kinases.
PLC-gamma associated with BLNK hydrolyzes phosphatidylinositol-4,5-bisphosphate to yield inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (Carter et al. 1991, Kim et al. 2004). IP3 binds receptors on the endoplasmic reticulum and causes release of calcium ions from the ER into the cytosol. The depletion of calcium from the ER in turn activates STIM1 to interact with ORAI and TRPC1 channels in the plasma membrane, resulting in an influx of extracellular calcium ions (Muik et al. 2008, Luik et al. 2008, Park et al. 2009, Mori et al. 2002). PI3K associated with BCAP and CD19 phosphorylates phosphatidylinositol 4,5-bisphosphate to yield phosphatidyinositol 3,4,5-trisphosphate.
Second messengers (calcium, diacylglycerol, inositol 1,4,5-trisphosphate, and phosphatidylinositol 3,4,5-trisphosphate) trigger signaling pathways: NF-kappaB is activated via protein kinase C beta, RAS is activated via RasGRP proteins, NF-AT is activated via calcineurin, and AKT (PKB) is activated via PDK1 (reviewed in Shinohara and Kurosaki 2009, Stone 2006).

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## Module 8

Pathway 1: hsa00061 (KEGG) Fatty acid biosynthesis

NA

Pathway 2: GO:0006633 (GO) fatty acid biosynthetic process

The chemical reactions and pathways resulting in the formation of a fatty acid, any of the aliphatic monocarboxylic acids that can be liberated by hydrolysis from naturally occurring fats and oils. Fatty acids are predominantly straight-chain acids of 4 to 24 carbon atoms, which may be saturated or unsaturated; branched fatty acids and hydroxy fatty acids also occur, and very long chain acids of over 30 carbons are found in waxes.

Pathway 3: GO:0042761 (GO) very long-chain fatty acid biosynthetic process

The chemical reactions and pathways resulting in the formation of a very long-chain fatty acid. A very long-chain fatty acid has an aliphatic tail containing more than 22 carbons.

Pathway 4: GO:0051790 (GO) short-chain fatty acid biosynthetic process

The chemical reactions and pathways resulting in the formation of a short-chain fatty acid. A short-chain fatty acid has an aliphatic tail containing fewer than 6 carbons

Pathway 5: hsa00020 (KEGG) Citrate cycle (TCA cycle)

The citrate cycle (TCA cycle, Krebs cycle) is an important aerobic pathway for the final steps of the oxidation of carbohydrates and fatty acids. The cycle starts with acetyl-CoA, the activated form of acetate, derived from glycolysis and pyruvate oxidation for carbohydrates and from beta oxidation of fatty acids. The two-carbon acetyl group in acetyl-CoA is transferred to the four-carbon compound of oxaloacetate to form the six-carbon compound of citrate. In a series of reactions two carbons in citrate are oxidized to CO2 and the reaction pathway supplies NADH for use in the oxidative phosphorylation and other metabolic processes. The pathway also supplies important precursor metabolites including 2-oxoglutarate. At the end of the cycle the remaining four-carbon part is transformed back to oxaloacetate. According to the genome sequence data, many organisms seem to lack genes for the full cycle [MD:M00009], but contain genes for specific segments [MD:M00010 M00011].

Pathway 6: hsa00062 (KEGG) Fatty acid elongation

NA

Pathway 7: R-HSA-75105 (Reactome) Fatty acyl-CoA biosynthesis

Fatty acyl-CoA biosynthesis involves following steps:
-Palmitate synthesis catalyzed by Acetyl-CoA carboxylase and Fatty acid synthase
-Conversion of palmitic acid to long chain fatty acids and
-Conversion of long chain fatty acids to fatty acyl-CoA by acyl-CoA synthases.

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}

## Module 9

Pathway 1: GO:0004674 (GO) protein serine/threonine kinase activity

Catalysis of the reactions: ATP + protein serine = ADP + protein serine phosphate, and ATP + protein threonine = ADP + protein threonine phosphate.

Pathway 2: GO:0070371 (GO) ERK1 and ERK2 cascade

A MAPK cascade containing at least the ERK1 or ERK2 MAP kinases. It starts with the activation of a MAP3K, and the consecutive activation of a MPK2K and of ERK1 or ERK2. The cascade can also contain an additional tier: the upstream MAP4K. The kinases in each tier phosphorylate and activate the kinase in the downstream tier. The ERK1/ERK2 cascade is activated by mitogens, growth factors, G protein-coupled receptors, and results in cellular responses such as cell proliferation, cell differentiation and development.

Pathway 3: hsa04010 (KEGG) MAPK signaling pathway

The mitogen-activated protein kinase (MAPK) cascade is a highly conserved module that is involved in various cellular functions, including cell proliferation, differentiation and migration. Mammals express at least four distinctly regulated groups of MAPKs, extracellular signal-related kinases (ERK)-1/2, Jun amino-terminal kinases (JNK1/2/3), p38 proteins (p38alpha/beta/gamma/delta) and ERK5, that are activated by specific MAPKKs: MEK1/2 for ERK1/2, MKK3/6 for the p38, MKK4/7 (JNKK1/2) for the JNKs, and MEK5 for ERK5. Each MAPKK, however, can be activated by more than one MAPKKK, increasing the complexity and diversity of MAPK signalling. Presumably each MAPKKK confers responsiveness to distinct stimuli. For example, activation of ERK1/2 by growth factors depends on the MAPKKK c-Raf, but other MAPKKKs may activate ERK1/2 in response to pro-inflammatory stimuli.

Pathway 4: GO:0098978 (GO) glutamatergic synapse

A synapse that uses glutamate as a neurotransmitter.

Pathway 5: GO:0006633 (GO) fatty acid biosynthetic process

The chemical reactions and pathways resulting in the formation of a fatty acid, any of the aliphatic monocarboxylic acids that can be liberated by hydrolysis from naturally occurring fats and oils. Fatty acids are predominantly straight-chain acids of 4 to 24 carbon atoms, which may be saturated or unsaturated; branched fatty acids and hydroxy fatty acids also occur, and very long chain acids of over 30 carbons are found in waxes.

Pathway 6: GO:0051153 (GO) regulation of striated muscle cell differentiation

Any process that modulates the frequency, rate or extent of striated muscle cell differentiation.

Pathway 7: hsa04120 (KEGG) Ubiquitin mediated proteolysis

Protein ubiquitination plays an important role in eukaryotic cellular processes. It mainly functions as a signal for 26S proteasome dependent protein degradation. The addition of ubiquitin to proteins being degraded is performed by a reaction cascade consisting of three enzymes, named E1 (ubiquitin activating enzyme), E2 (ubiquitin conjugating enzyme), and E3 (ubiquitin ligase). Each E3 has specificity to its substrate, or proteins to be targeted by ubiquitination. Many E3s are discovered in eukaryotes and they are classified into four types: HECT type, U-box type, single RING-finger type, and multi-subunit RING-finger type. Multi-subunit RING-finger E3s are exemplified by cullin-Rbx E3s and APC/C. They consist of a RING-finger-containing subunit (RBX1 or RBX2) that functions to bind E2s, a scaffold-like cullin molecule, adaptor proteins, and a target recognizing subunit that binds substrates.

Expected JSON Output Format:

{
"module\_name": "Your concise module name here",
"summary": "A detailed, literature-integrated explanation of the module's function, key genes/proteins, and relevant biological processes.",
"confidence\_score": "A value between 0.00 and 1.00"
}

## Module 10

Pathway 1: GO:0004707 (GO) MAP kinase activity

Catalysis of the reaction: protein + ATP = protein phosphate + ADP. This reaction is the phosphorylation of proteins. Mitogen-activated protein kinase; a family of protein kinases that perform a crucial step in relaying signals from the plasma membrane to the nucleus. They are activated by a wide range of proliferation- or differentiation-inducing signals; activation is strong with agonists such as polypeptide growth factors and tumor-promoting phorbol esters, but weak (in most cell backgrounds) by stress stimuli.

Pathway 2: R-HSA-69306 (Reactome) DNA Replication

Studies in the past decade have suggested that the basic mechanism of DNA replication initiation is conserved in all kingdoms of life. Initiation in unicellular eukaryotes, in particular Saccharomyces cerevisiae (budding yeast), is well understood, and has served as a model for studies of DNA replication initiation in multicellular eukaryotes, including humans. In general terms, the first step of initiation is the binding of the replication initiator to the origin of replication. The replicative helicase is then assembled onto the origin, usually by a helicase assembly factor. Either shortly before or shortly after helicase assembly, some local unwinding of the origin of replication occurs in a region rich in adenine and thymine bases (often termed a DNA unwinding element, DUE). The unwound region provides the substrate for primer synthesis and initiation of DNA replication. The best-defined eukaryotic origins are those of S. cerevisiae, which have well-conserved sequence elements for initiator binding, DNA unwinding and binding of accessory proteins. In multicellular eukaryotes, unlike S. cerevisiae, these loci appear not to be defined by the presence of a DNA sequence motif. Indeed, choice of replication origins in a multicellular eukaryote may vary with developmental stage and tissue type. In cell-free models of metazoan DNA replication, such as the one provided by Xenopus egg extracts, there are only limited DNA sequence specificity requirements for replication initiation (Kelly & Brown 2000; Bell & Dutta 2002; Marahrens & Stillman 1992; Cimbora & Groudine 2001; Mahbubani et al 1992, Hyrien & Mechali 1993).

Pathway 3: R-HSA-983705 (Reactome) Signaling by the B Cell Receptor (BCR)

Mature B cells express IgM and IgD immunoglobulins which are complexed at the plasma membrane with Ig-alpha (CD79A, MB-1) and Ig-beta (CD79B, B29) to form the B cell receptor (BCR) (Fu et al. 1974, Fu et al. 1975, Kunkel et al. 1975, Van Noesel et al. 1992, Sanchez et al. 1993, reviewed in Brezski and Monroe 2008). Binding of antigen to the immunoglobulin activates phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) in the cytoplasmic tails of Ig-alpha and Ig-beta by Src family tyrosine kinases, including LYN, FYN, and BLK (Nel et al. 1984, Yamanashi et al. 1991, Flaswinkel and Reth 1994, Saouaf et al. 1994, Hata et al. 1994, Saouaf et al. 1995, reviewed in Gauld and Cambier 2004, reviewed in Harwood and Batista 2010).
The protein kinase SYK binds the phosphorylated immunoreceptor tyrosine-activated motifs (ITAMs) on the cytoplasmic tails of Ig-alpha (CD79A, MB-1) and Ig-beta (CD79B, B29) (Wienands et al. 1995, Rowley et al. 1995, Tsang et al. 2008). The binding causes the activation and autophosphorylation of SYK (Law et al. 1994, Baldock et al. 2000, Irish et al. 2006, Tsang et al. 2008, reviewed in Bradshaw 2010).
Activated SYK and other kinases phosphorylate BLNK (SLP-65), BCAP, and CD19 which serve as scaffolds for the assembly of large complexes, the signalosomes, by recruiting phosphoinositol 3-kinase (PI3K), phospholipase C gamma (predominantly PLC-gamma2 in B cells, Coggeshall et al. 1992), NCK, BAM32, BTK, VAV1, and SHC. The effectors are phosphorylated by SYK and other kinases.
PLC-gamma associated with BLNK hydrolyzes phosphatidylinositol-4,5-bisphosphate to yield inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (Carter et al. 1991, Kim et al. 2004). IP3 binds receptors on the endoplasmic reticulum and causes release of calcium ions from the ER into the cytosol. The depletion of calcium from the ER in turn activates STIM1 to interact with ORAI and TRPC1 channels in the plasma membrane, resulting in an influx of extracellular calcium ions (Muik et al. 2008, Luik et al. 2008, Park et al. 2009, Mori et al. 2002). PI3K associated with BCAP and CD19 phosphorylates phosphatidylinositol 4,5-bisphosphate to yield phosphatidyinositol 3,4,5-trisphosphate.
Second messengers (calcium, diacylglycerol, inositol 1,4,5-trisphosphate, and phosphatidylinositol 3,4,5-trisphosphate) trigger signaling pathways: NF-kappaB is activated via protein kinase C beta, RAS is activated via RasGRP proteins, NF-AT is activated via calcineurin, and AKT (PKB) is activated via PDK1 (reviewed in Shinohara and Kurosaki 2009, Stone 2006).

Pathway 4: hsa00062 (KEGG) Fatty acid elongation

NA

Pathway 5: GO:0051148 (GO) negative regulation of muscle cell differentiation

Any process that stops, prevents, or reduces the frequency, rate or extent of muscle cell differentiation.

Expected JSON Output Format:

{
"module\_name": "Your concise module name here",
"summary": "A detailed, literature-integrated explanation of the module's function, key genes/proteins, and relevant biological processes.",
"confidence\_score": "A value between 0.00 and 1.00"
}

## Module 11

Pathway 1: GO:0000165 (GO) MAPK cascade

An intracellular protein kinase cascade containing at least a MAP kinase (MAPK). It starts with the activation of a MAP3K, and the consecutive activation of a MPK2K and a MAPK. The cascade can also contain an additional tier: the upstream MAP4K. The kinases in each tier phosphorylate and activate the kinase in the downstream tier to transmit a signal within a cell.

Pathway 2: hsa00190 (KEGG) Oxidative phosphorylation

NA

Pathway 3: hsa04660 (KEGG) T cell receptor signaling pathway

Activation of T lymphocytes is a key event for an efficient response of the immune system. It requires the involvement of the T-cell receptor (TCR) as well as costimulatory molecules such as CD28. Engagement of these receptors through the interaction with a foreign antigen associated with major histocompatibility complex molecules and CD28 counter-receptors B7.1/B7.2, respectively, results in a series of signaling cascades. These cascades comprise an array of protein-tyrosine kinases, phosphatases, GTP-binding proteins and adaptor proteins that regulate generic and specialised functions, leading to T-cell proliferation, cytokine production and differentiation into effector cells.

Pathway 4: hsa00020 (KEGG) Citrate cycle (TCA cycle)

The citrate cycle (TCA cycle, Krebs cycle) is an important aerobic pathway for the final steps of the oxidation of carbohydrates and fatty acids. The cycle starts with acetyl-CoA, the activated form of acetate, derived from glycolysis and pyruvate oxidation for carbohydrates and from beta oxidation of fatty acids. The two-carbon acetyl group in acetyl-CoA is transferred to the four-carbon compound of oxaloacetate to form the six-carbon compound of citrate. In a series of reactions two carbons in citrate are oxidized to CO2 and the reaction pathway supplies NADH for use in the oxidative phosphorylation and other metabolic processes. The pathway also supplies important precursor metabolites including 2-oxoglutarate. At the end of the cycle the remaining four-carbon part is transformed back to oxaloacetate. According to the genome sequence data, many organisms seem to lack genes for the full cycle [MD:M00009], but contain genes for specific segments [MD:M00010 M00011].

Pathway 5: R-HSA-8852135 (Reactome) Protein ubiquitination

Ubiquitin is a small, 76 amino acid residue protein that is conjugated by E3 ubiquitin ligases to other proteins in order to regulate their function or degradation (enzymatic cascade reviewed in Neutzner and Neutzner 2012, Kleiger and Mayor 2014, structures and mechanisms of conjugating enzymes reviewed in Lorenz et al. 2013). Ubiquitination of target proteins usually occurs between the C-terminal glycine residue of ubiquitin and a lysine residue of the target, although linkages with cysteine, serine, and threonine residues are also observed (reviewed in Wang et al. 2012, McDowell and Philpott 2013).
Ubiquitin must first be processed from larger precursors and then activated by formation of a thiol ester bond between ubiquitin and an E1 activating enzyme (UBA1 or UBA6) and transfer to an E2 conjugating enzyme before being transferred by an E3 ligase to a target protein. Precursor proteins containing multiple ubiquitin monomers (polyubiquitins) are produced from the UBB and UBC genes; precursors containing a single ubiquitin monomer and a ribosomal protein are produced from the UBA52 and RPS27A genes. Many proteases (deubiquitinases) may potentially process these precursors yielding monomeric ubiquitin. The proteases OTULIN and USP5 are particularly active in cleaving the polyubiquitin precursors, whereas the proteases UCHL3, USP7, and USP9X cleave the ubiquitin-ribosomal protein precursors yielding ubiquitin monomers (Grou et al. 2015). A resultant ubiquitin monomer is activated by adenylation of the C-terminal glycine followed by conjugation of the C-terminus to a cysteine residue of the E1 enzymes UBA1 or UBA6 via a thiol ester bond. The ubiquitin is then transferred from the E1 enzyme to a cysteine residue of one of several E2 enzymes (reviewed in van Wijk and Timmers 2010, Stewart et al. 2016). Through a less well characterized mechanism, E3 ubiquitin ligases then bring a target protein and the E2-ubiquitin conjugate into proximity so that the ubiquitin is transferred via formation of an amide bond to a particular lysine residue (or, in rarer cases, a thiol ester bond to a cysteine residue or an ester bond to a serine or threonine residue) of the target protein (reviewed in Berndsen and Wolberger 2014). Based on protein homologies, families of E3 ubiquitin ligases have been identified that include RING-type ligases (reviewed in Deshaies et al. 2009, Metzger et al. 2012, Metzger et al. 2014), HECT-type ligases (reviewed in Rotin et al. 2009, Metzger et al. 2012), and RBR-type ligases (reviewed in Dove et al. 2016). A subset of the RING-type ligases participate in CULLIN-RING ligase complexes (CRLs which include SCF complexes, reviewed in Lee and Zhou 2007, Genschik et al. 2013, Skaar et al. 2013, Lee et al. 2014).
Some E3-E2 combinations catalyze mono-ubiquitination of the target protein (reviewed in Nakagawa and Nakayama 2015). Other E3-E2 combinations catalyze conjugation of further ubiquitin monomers to the initial ubiquitin, forming polyubiquitin chains. (It may also be possible for some E3-E2 combinations to preassemble polyubiquitin and transfer it as a unit to the target protein.) Ubiquitin contains several lysine (K) residues and a free alpha amino group to which further ubiquitin can be conjugated. Thus different types of polyubiquitin are possible: K11 linked polyubiquitin is observed in endoplasmic reticulum-associated degradation (ERAD), K29 linked polyubiquitin is observed in lysosomal degradation, K48 linked polyubiquitin directs target proteins to the proteasome for degradation, whereas K63 linked polyubiquitin generally acts as a scaffold to recruit other proteins in several cellular processes, notably DNA repair (reviewed in Komander et al. 2009). Ubiquitination is highly regulated (reviewed in Vittal et al. 2015) and affects all cellular processes including DNA damage response (reviewed in Brown and Jackson 2015), immune signaling (reviewed in Park et al. 2014, Lutz-Nicoladoni et al. 2015), and regulation of normal and cancerous cell growth (reviewed in Skaar and Pagano 2009, Yerlikaya and Yontem 2013, Strikoudis et al. 2014).

Expected JSON Output Format:

{
"module\_name": "Your concise module name here",
"summary": "A detailed, literature-integrated explanation of the module's function, key genes/proteins, and relevant biological processes.",
"confidence\_score": "A value between 0.00 and 1.00"
}

## Module 12

Pathway 1: R-HSA-68952 (Reactome) DNA replication initiation

DNA polymerases are not capable of de novo DNA synthesis and require synthesis of a primer, usually by a DNA-dependent RNA polymerase (primase) to begin DNA synthesis. In eukaryotic cells, the primer is synthesized by DNA polymerase alpha:primase. First, the DNA primase portion of this complex synthesizes approximately 6-10 nucleotides of RNA primer and then the DNA polymerase portion synthesizes an additional 20 nucleotides of DNA (Frick & Richardson 2002; Wang et al 1984).

Pathway 2: GO:0051790 (GO) short-chain fatty acid biosynthetic process

The chemical reactions and pathways resulting in the formation of a short-chain fatty acid. A short-chain fatty acid has an aliphatic tail containing fewer than 6 carbons

Pathway 3: GO:0051147 (GO) regulation of muscle cell differentiation

Any process that modulates the frequency, rate or extent of muscle cell differentiation.

Expected JSON Output Format:

{
"module\_name": "Your concise module name here",
"summary": "A detailed, literature-integrated explanation of the module's function, key genes/proteins, and relevant biological processes.",
"confidence\_score": "A value between 0.00 and 1.00"
}

## Module 13

Pathway 1: GO:0045251 (GO) electron transfer flavoprotein complex

A protein complex facilitating the electron transfer from an acyl-CoA molecule to ubiquinone via its flavin adenine dinucleotide (FAD) cofactor. Usually contains an alpha and a beta subunit and the structural cofactor adenosine monophosphate (AMP). Part of a system that oxidizes an acyl-CoA molecule and reduces ubiquinone and other acceptors in the electron transport system.

Pathway 2: GO:0006955 (GO) immune response

Any immune system process that functions in the calibrated response of an organism to a potential internal or invasive threat.

Pathway 3: GO:0051154 (GO) negative regulation of striated muscle cell differentiation

Any process that stops, prevents, or reduces the frequency, rate or extent of striated muscle cell differentiation.

Expected JSON Output Format:

{
"module\_name": "Your concise module name here",
"summary": "A detailed, literature-integrated explanation of the module's function, key genes/proteins, and relevant biological processes.",
"confidence\_score": "A value between 0.00 and 1.00"
}

## Module 14

Pathway 1: hsa03030 (KEGG) DNA replication

A complex network of interacting proteins and enzymes is required for DNA replication. Generally, DNA replication follows a multistep enzymatic pathway. At the DNA replication fork, a DNA helicase (DnaB or MCM complex) precedes the DNA synthetic machinery and unwinds the duplex parental DNA in cooperation with the SSB or RPA. On the leading strand, replication occurs continuously in a 5 to 3 direction, whereas on the lagging strand, DNA replication occurs discontinuously by synthesis and joining of short Okazaki fragments. In prokaryotes, the leading strand replication apparatus consists of a DNA polymerase (pol III core), a sliding clamp (beta), and a clamp loader (gamma delta complex). The DNA primase (DnaG) is needed to form RNA primers. Normally, during replication of the lagging-strand DNA template, an RNA primer is removed either by an RNase H or by the 5 to 3 exonuclease activity of DNA pol I, and the DNA ligase joins the Okazaki fragments. In eukaryotes, three DNA polymerases (alpha, delta, and epsilon) have been identified. DNA primase forms a permanent complex with DNA polymerase alpha. PCNA and RFC function as a clamp and a clamp loader. FEN 1 and RNase H1 remove the RNA from the Okazaki fragments and DNA ligase I joins the DNA.

Pathway 2: hsa00061 (KEGG) Fatty acid biosynthesis

NA

Pathway 3: GO:0016567 (GO) protein ubiquitination

The process in which one or more ubiquitin groups are added to a protein.

Expected JSON Output Format:

{
"module\_name": "Your concise module name here",
"summary": "A detailed, literature-integrated explanation of the module's function, key genes/proteins, and relevant biological processes.",
"confidence\_score": "A value between 0.00 and 1.00"
}

## Module 15

Pathway 1: hsa04724 (KEGG) Glutamatergic synapse

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system(CNS). Glutamate is packaged into synaptic vesicles in the presynaptic terminal. Once released into the synaptic cleft, glutamate acts on postsynaptic ionotropic glutamate receptors (iGluRs) to mediate fast excitatory synaptic transmission. Glutamate can also act on metabotropic glutamate receptors (mGluRs) and exert a variety of modulatory effects through their coupling to G proteins and the subsequent recruitment of second messenger systems. Presynaptically localized Group II and Group III mGluRs are thought to represent the classical inhibitory autoreceptor mechanism that suppresses excess glutamate release. After its action on these receptors, glutamate can be removed from the synaptic cleft by EAATs located either on the presynaptic terminal, neighboring glial cells, or the postsynaptic neuron. In glia, glutamate is converted to glutamine, which is then transported back to the presynaptic terminal and converted back to glutamate.

Pathway 2: GO:0009055 (GO) electron transfer activity

A molecular function representing the directed movement of electrons from one molecular entity to another, typically mediated by electron carriers or acceptors, resulting in the transfer of energy and/or the reduction-oxidation (redox) transformation of chemical species. This activity is fundamental to various biological processes, including cellular respiration and photosynthesis, as well as numerous enzymatic reactions involved in metabolic pathways.

Pathway 3: GO:0002250 (GO) adaptive immune response

An immune response mediated by cells expressing specific receptors for antigens produced through a somatic diversification process, and allowing for an enhanced secondary response to subsequent exposures to the same antigen (immunological memory).

Pathway 4: hsa04662 (KEGG) B cell receptor signaling pathway

B cells are an important component of adaptive immunity. They produce and secrete millions of different antibody molecules, each of which recognizes a different (foreign) antigen. The B cell receptor (BCR) is an integral membrane protein complex that is composed of two immunoglobulin (Ig) heavy chains, two Ig light chains and two heterodimers of Ig-alpha and Ig-beta. After BCR ligation by antigen, three main protein tyrosine kinases (PTKs) -the SRC-family kinase LYN, SYK and the TEC-family kinase BTK- are activated. Phosphatidylinositol 3-kinase (PI3K) and phospholipase C-gamma 2 (PLC-gamma 2) are important downstream effectors of BCR signalling. This signalling ultimately results in the expression of immediate early genes that further activate the expression of other genes involved in B cell proliferation, differentiation and Ig production as well as other processes.

Pathway 5: R-HSA-388841 (Reactome) Regulation of T cell activation by CD28 family

Optimal activation of T lymphocytes requires a carefully orchestrated interplay between two key signals. The first signal originates from the T cell receptor (TCR) recognizing a specific antigen. However, this initial encounter is insufficient on its own. A crucial "costimulatory" signal is needed for full T cell activation, delivered by the engagement of costimulatory receptors, such as CD28, on the T cell surface with their corresponding ligands on antigen-presenting cells (APCs) (Chen & Flies 2013, Acuto et al. 2003, Slavik et al. 1999).
The CD28 superfamily is central to costimulation, encompassing a diverse group of receptors including CD28, CTLA-4, ICOS, PD-1, and BTLA. These receptors have both positive and negative influences on T cell activation. CD28 and ICOS provide a positive boost, while CTLA-4, PD-1, and BTLA act as inhibitory brakes. CD28 and CTLA-4 bind to B7 family ligands CD80 (B7.1) and CD86 (B7.2), with CD28 delivering stimulatory signals and CTLA-4 providing inhibitory signals. ICOS interacts with ICOS ligand (ICOS-L), enhancing T cell activation and function. PD-1 binds to PD-L1 and PD-L2, mediating inhibitory signals that modulate the immune response. BTLA engages with HVEM (Herpesvirus entry mediator), transmitting inhibitory signals. This balance between stimulatory and inhibitory signals is essential, allowing the immune system to mount effective responses against pathogens while preventing the induction of T cell unresponsiveness and apoptosis (Chen & Flies 2013, Sharpe & Freeman 2002, Carreno & Collins 2002).
The expression of these receptors varies: CD28 is constantly present on naive T cells, whereas CTLA-4 expression depends on prior CD28 engagement. ICOS, PD-1, and BTLA are induced only after initial T cell stimulation. These variations in expression ensure precise regulation of T cell responses at different stages of activation (Sharpe & Freeman 2002). The receptors themselves also exhibit structural differences. CD28, CTLA-4, and ICOS share a single extracellular domain resembling an immunoglobulin molecule (IgV-like). In contrast, BTLA has a distinct structure with an IgC-like domain. Similarly, the costimulatory ligands, such as B7-1 and B7-2, have unique structural features that enable specific interactions with their partner receptors

Pathway 6: GO:0042761 (GO) very long-chain fatty acid biosynthetic process

The chemical reactions and pathways resulting in the formation of a very long-chain fatty acid. A very long-chain fatty acid has an aliphatic tail containing more than 22 carbons.

Pathway 7: R-HSA-75105 (Reactome) Fatty acyl-CoA biosynthesis

Fatty acyl-CoA biosynthesis involves following steps:
-Palmitate synthesis catalyzed by Acetyl-CoA carboxylase and Fatty acid synthase
-Conversion of palmitic acid to long chain fatty acids and
-Conversion of long chain fatty acids to fatty acyl-CoA by acyl-CoA synthases.

Expected JSON Output Format:

{
"module\_name": "Your concise module name here",
"summary": "A detailed, literature-integrated explanation of the module's function, key genes/proteins, and relevant biological processes.",
"confidence\_score": "A value between 0.00 and 1.00"
}

## Module 16

Pathway 1: hsa04210 (KEGG) Apoptosis

Apoptosis is a genetically programmed process for the elimination of damaged or redundant cells by activation of caspases (aspartate-specific cysteine proteases). The onset of apoptosis is controlled by numerous interrelating processes. The 'extrinsic' pathway involves stimulation of members of the tumor necrosis factor (TNF) receptor subfamily, such as TNFRI, CD95/Fas or TRAILR (death receptors), located at the cell surface, by their specific ligands, such as TNF-alpha, FasL or TRAIL, respectively. The 'intrinsic' pathway is activated mainly by non-receptor stimuli, such as DNA damage, ER stress, metabolic stress, UV radiation or growth-factor deprivation. The central event in the 'intrinsic' pathway is the mitochondrial outer membrane permeabilization (MOMP), which leads to the release of cytochrome c. These two pathways converge at the level of effector caspases, such as caspase-3 and caspase-7. The third major pathway is initiated by the constituents of cytotoxic granules (e.g. Perforin and Granzyme B) that are released by CTLs (cytotoxic T-cells) and NK (natural killer) cells. Granzyme B, similarly to the caspases, cleaves its substrates after aspartic acid residues, suggesting that this protease has the ability to activate members of the caspase family directly. It is the balance between the pro-apoptotic and anti-apoptotic signals that eventually determines whether cells will undergo apoptosis, survive or proliferate. TNF family of ligands activates anti-apoptotic or cell-survival signals as well as apoptotic signals. NGF and Interleukin-3 promotes the survival, proliferation and differentiation of neurons or hematopoietic cells, respectively. Withdrawal of these growth factors leads to cell death, as described above.

Pathway 2: GO:0004672 (GO) protein kinase activity

Catalysis of the phosphorylation of an amino acid residue in a protein, usually according to the reaction: a protein + ATP = a phosphoprotein + ADP.

Pathway 3: GO:0098985 (GO) asymmetric, glutamatergic, excitatory synapse

A neuron to neuron synapse with a postsynaptic density, that uses glutamate as a neurotransmitter and whose activity results in excitatory postsynaptic potentials.

Pathway 4: R-HSA-1280218 (Reactome) Adaptive Immune System

Adaptive immunity refers to antigen-specific immune response efficiently involved in clearing the pathogens. The adaptive immune system is comprised of B and T lymphocytes that express receptors with remarkable diversity tailored to recognize aspects of particular pathogens or antigens. During infection, dendritic cells (DC) which act as sentinels in the peripheral tissues recognize and pick up the pathogen in the form of antigenic determinants and then process these antigens and present them to T cells. These T cells of appropriate specificity respond to the antigen, and either kill the pathogen directly or secrete cytokines that will stimulate B lymphocyte response. B cells provide humoral immunity by secreting antibodies specific for the pathogen or antigen.

Pathway 5: GO:0051146 (GO) striated muscle cell differentiation

The process in which a relatively unspecialized cell acquires specialized features of a striated muscle cell; striated muscle fibers are divided by transverse bands into striations, and cardiac and voluntary muscle are types of striated muscle.

Pathway 6: hsa03050 (KEGG) Proteasome

The proteasome is a protein-destroying apparatus involved in many essential cellular functions, such as regulation of cell cycle, cell differentiation, signal transduction pathways, antigen processing for appropriate immune responses, stress signaling, inflammatory responses, and apoptosis. It is capable of degrading a variety of cellular proteins in a rapid and timely fashion and most substrate proteins are modified by ubiquitin before their degradation by the proteasome. The proteasome is a large protein complex consisting of a proteolytic core called the 20S particle and ancillary factors that regulate its activity in various ways. The most common form is the 26S proteasome containing one 20S core particle and two 19S regulatory particles that enable the proteasome to degrade ubiquitinated proteins by an ATP-dependent mechanism. Another form is the immunoproteasome containing two 11S regulatory particles, PA28 alpha and PA28 beta, which are induced by interferon gamma under the conditions of intensified immune response. Other regulatory particles include PA28 gamma and PA200. Although PA28 gamma also belongs to a family of activators of the 20S proteasome, it is localized within the nucleus and forms a homoheptamer. PA28 gamma has been implicated in the regulation of cell cycle progression and apoptosis. PA200 has been identified as a large nuclear protein that stimulates proteasomal hydrolysis of peptides.

Pathway 7: GO:0061630 (GO) ubiquitin protein ligase activity

Catalysis of the transfer of ubiquitin to a substrate protein via the reaction X-ubiquitin + S = X + S-ubiquitin, where X is either an E2 or E3 enzyme, the X-ubiquitin linkage is a thioester bond, and the S-ubiquitin linkage is an amide bond: an isopeptide bond between the C-terminal glycine of ubiquitin and the epsilon-amino group of lysine residues in the substrate or, in the linear extension of ubiquitin chains, a peptide bond the between the C-terminal glycine and N-terminal methionine of ubiquitin residues.

Expected JSON Output Format:

{
"module\_name": "Your concise module name here",
"summary": "A detailed, literature-integrated explanation of the module's function, key genes/proteins, and relevant biological processes.",
"confidence\_score": "A value between 0.00 and 1.00"
}