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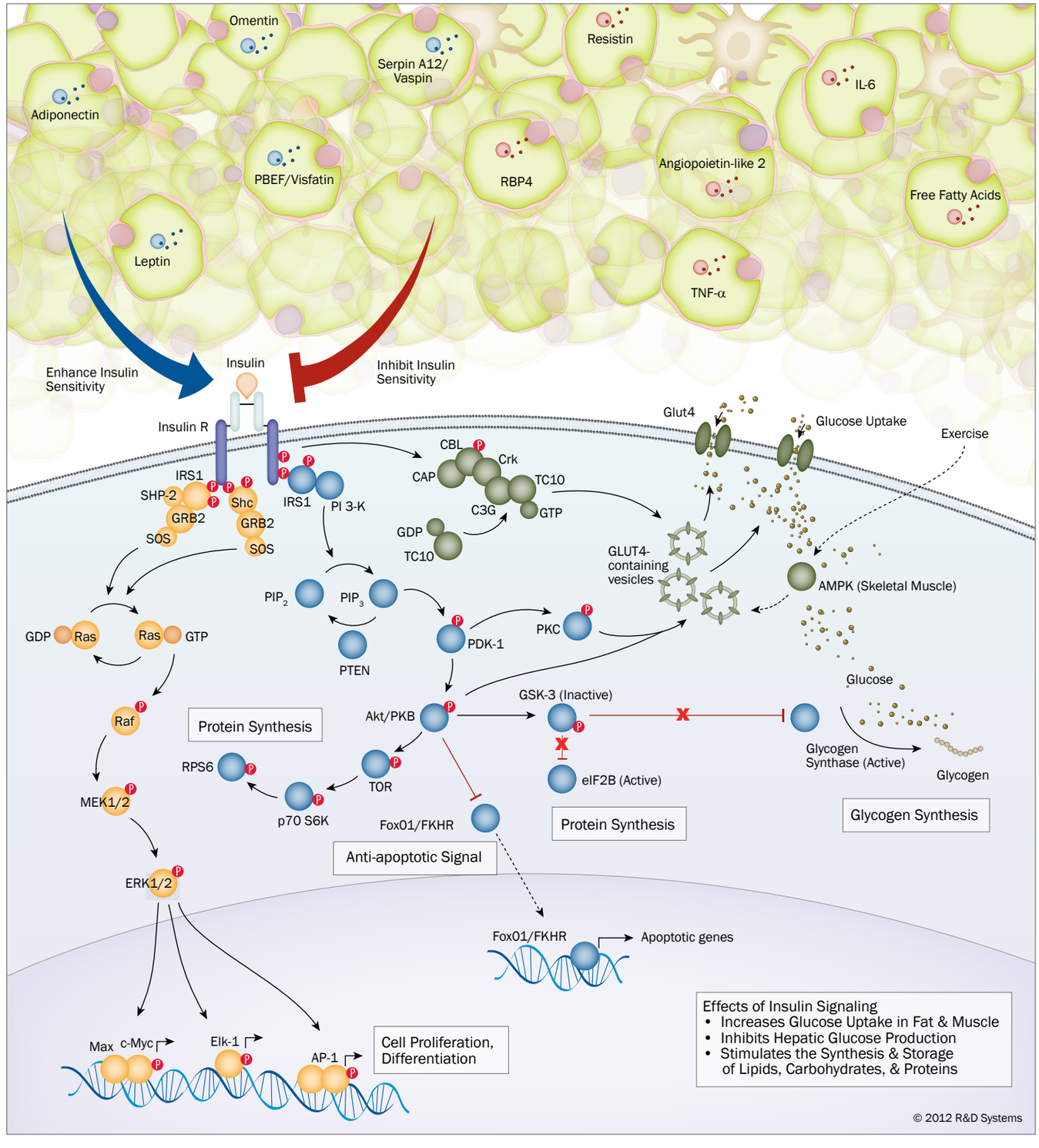
The Effects of Adipocytokines on Insulin Signaling Pathways

Insulin, secreted by the pancreatic β cells, is the main regulator of blood glucose levels. It inhibits glucose production in the liver, stimulates glucose uptake in muscle and fat, promotes glycogen and lipid synthesis, and inhibits lipolysis. Insulin signaling promotes glucose uptake by activating intracellular signaling pathways that promote translocation of the GLUT4 glucose transporter to the plasma membrane. Additionally, insulin signaling inactivates GSK-3, which keeps Glycogen Synthase active, thereby promoting the storage of glucose as glycogen. Insulin signaling can be enhanced or inhibited by adipocytokines secreted by the adipose tissue. The ability of these cytokines to influence insulin signaling suggests that changes in their levels may contribute to the development of insulin-related metabolic disorders such as Type II diabetes. In support of this hypothesis, one of the leading risk factors for Type II diabetes is obesity, a condition characterized by an increase in adipose tissue mass, altered adipocytokine secretion, and chronic inflammation. Obesity is associated with reduced Leptin sensitivity and decreased Adiponectin production, two adipocytokines that normally enhance insulin sensitivity. These changes are coupled with an increase in the production of pro-inflammatory cytokines such as TNF-α and IL-6, which can negatively affect adipose tissue functions and promote insulin resistance. Characterizing the mechanisms by which adipocytokines enhance or interfere with insulin signaling pathways is critical to our understanding of how these factors may contribute to the pathogenesis of metabolic disorders.

Interact with this pathway | rndsystems.com/pathways_adipokine_insulin



January

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December 2016

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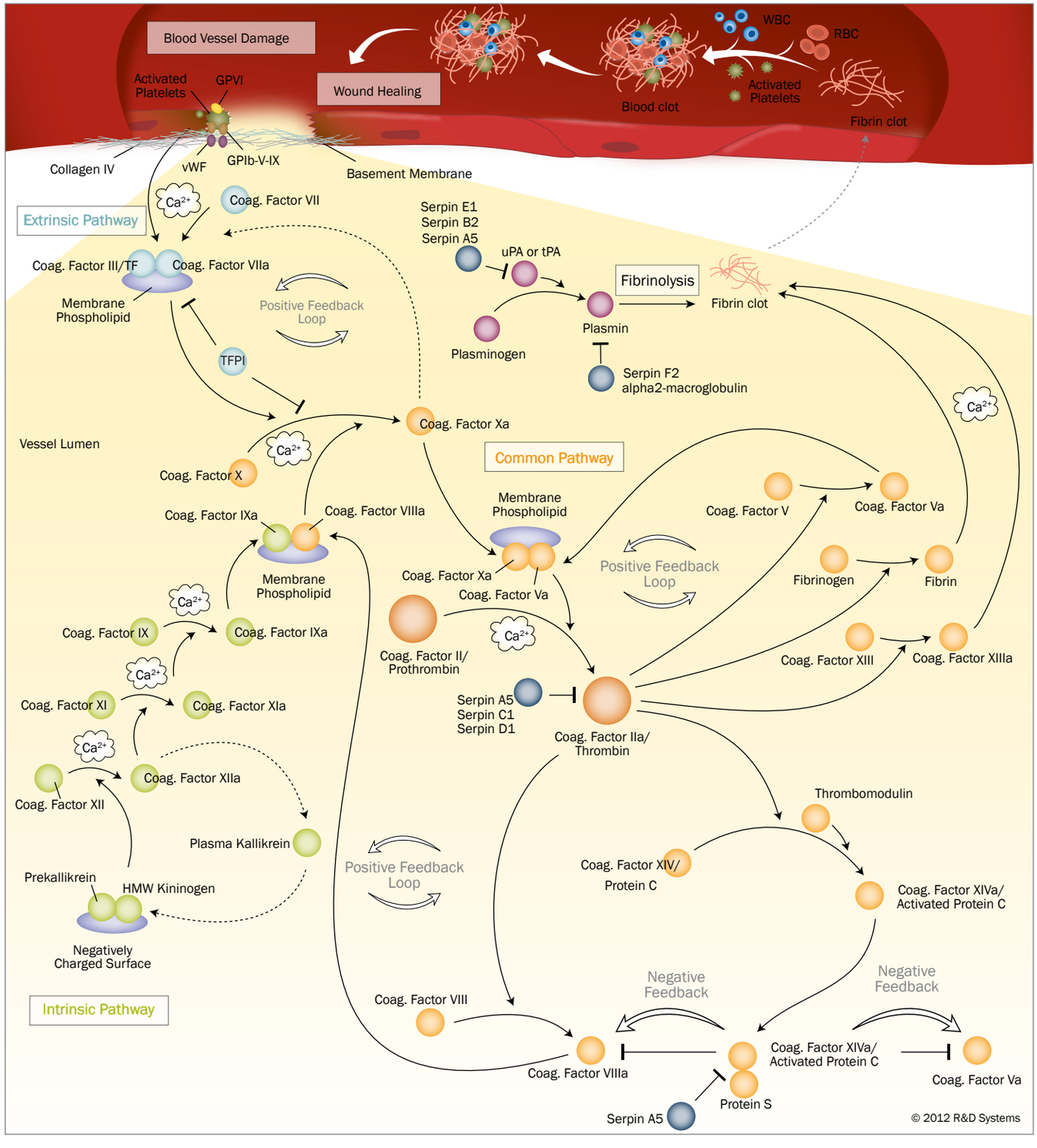
The Extrinsic and Intrinsic Pathways of Blood Coagulation

Injuries that damage blood vessels promote blood coagulation, a rapid response to initiate hemostasis and protect the host from excessive blood loss. Blood coagulation results from a series of proteolytic reactions involving the step-wise activation of coagulation factors. Subsets of these factors can be activated by two distinct pathways, the extrinsic or tissue damage pathway, and the intrinsic or contact pathway. Each pathway is initiated by different factors, but both converge upon a single common pathway that leads to the activation of Coagulation Factor Xa, and the conversion of Prothrombin/Coagulation Factor II to active Thrombin/Coagulation Factor IIa. Thrombin converts Fibrinogen to Fibrin monomers which polymerize to form a Fibrin clot. The Fibrin clot acts in concert with activated platelets at the site of the injury to form a blood clot that stabilizes the damaged tissue and prevents further blood loss.

In addition to generating active Fibrin and Coagulation Factor XIIIa, Thrombin/Coagulation Factor IIa activates Coagulation Factors V, VIII, and Protein C. These factors enhance or inhibit Thrombin production through positive or negative feedback regulation. This feedback regulation, along with the sequential activation of clotting factors, allows precise control of the blood coagulation cascade, which is critical to prevent excessive blood loss associated with too little clotting, or too much clotting, which could result in blockage of a blood vessel and lead to a heart attack or stroke.

Interact with this pathway | rndsystems.com/pathways_bloodcoagulation



February

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26	27	28 Linus Pauling Day				

January

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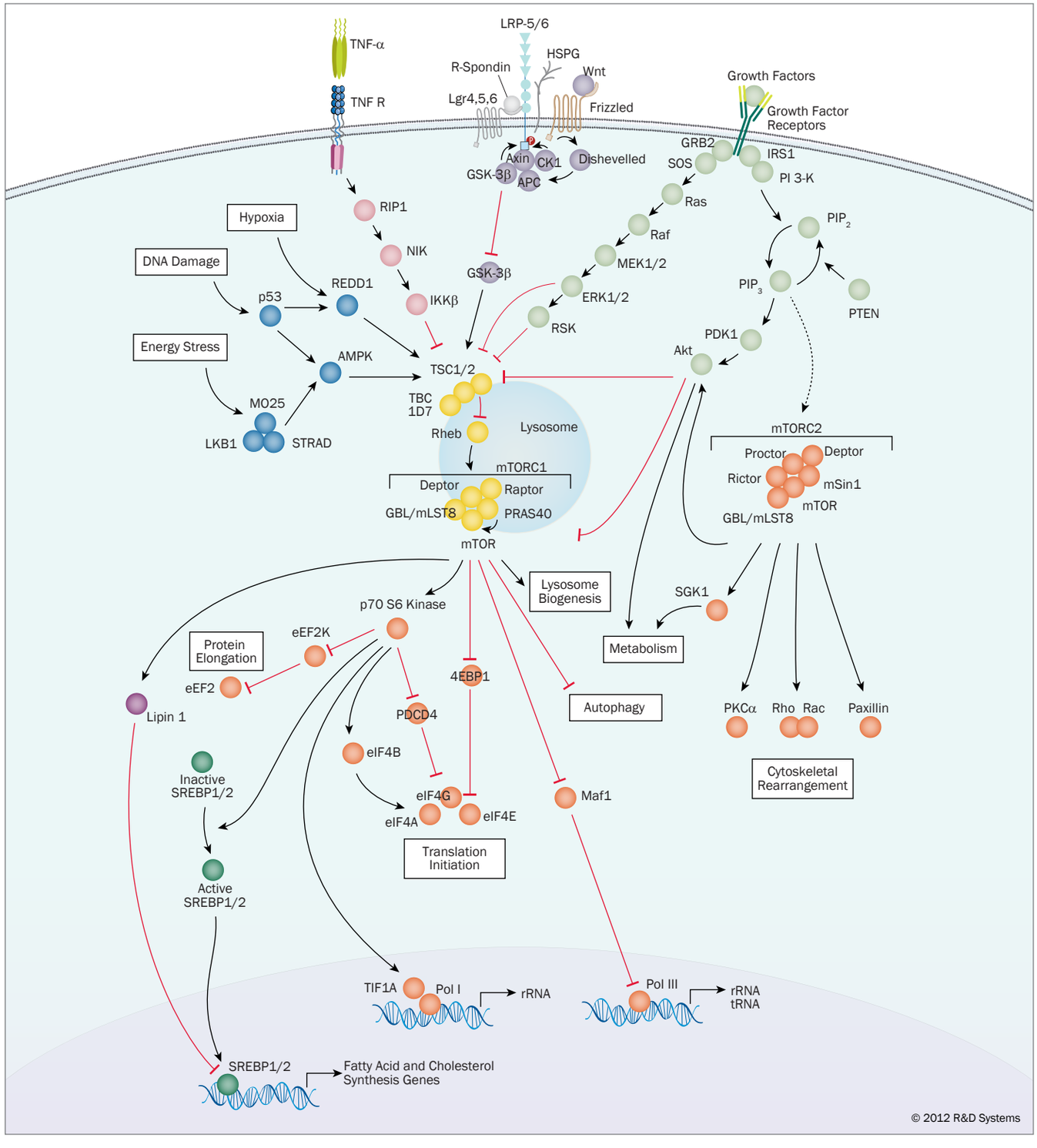
mTOR Signaling Pathways

The mammalian Target of Rapamycin (mTOR) complex is the central cellular regulator of anabolic and catabolic cellular metabolism and survival. mTOR forms at least two distinct multiprotein complexes (mTORCs) with additional regulatory proteins. The mTOR Complex 1 (mTORC1) includes mTOR, Raptor, PRAS40, Deptor, and GBL/mLST8, while mTORC2 includes mTOR, Rictor, mSin1, Proctor/PRR5, Deptor, and GBL/mLST8. mTOR activity is regulated in response to both extracellular and intracellular cues. Extracellular signaling factors include Wnts, TNF-α, and growth factors, which signal through a variety of intracellular pathways to regulate TSC1/2 and mTORC1 activity, or mTORC2. In addition to responding to extracellular cues, mTORC1 activity is also regulated by intracellular cues including energy availability, oxygen levels, and amino acid availability. In the presence of available amino acids, mTORC1 is recruited to the lysosomal membrane where it initiates anabolic activities including protein synthesis, lipid synthesis, autophagy, mitochondrial metabolism, and biogenesis. Less is known about the upstream signals and cellular functions that regulate mTORC2. mTORC2 activity is strongly correlated with Akt activity. mTORC2 has been shown to regulate cytoskeletal rearrangement, as well as cell survival and proliferation.



Interact with this pathway | rndsystems.com/pathways_mtor

March

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26 Jonas Salk Announces Polio Vaccine	27	28	29	30	31	

February

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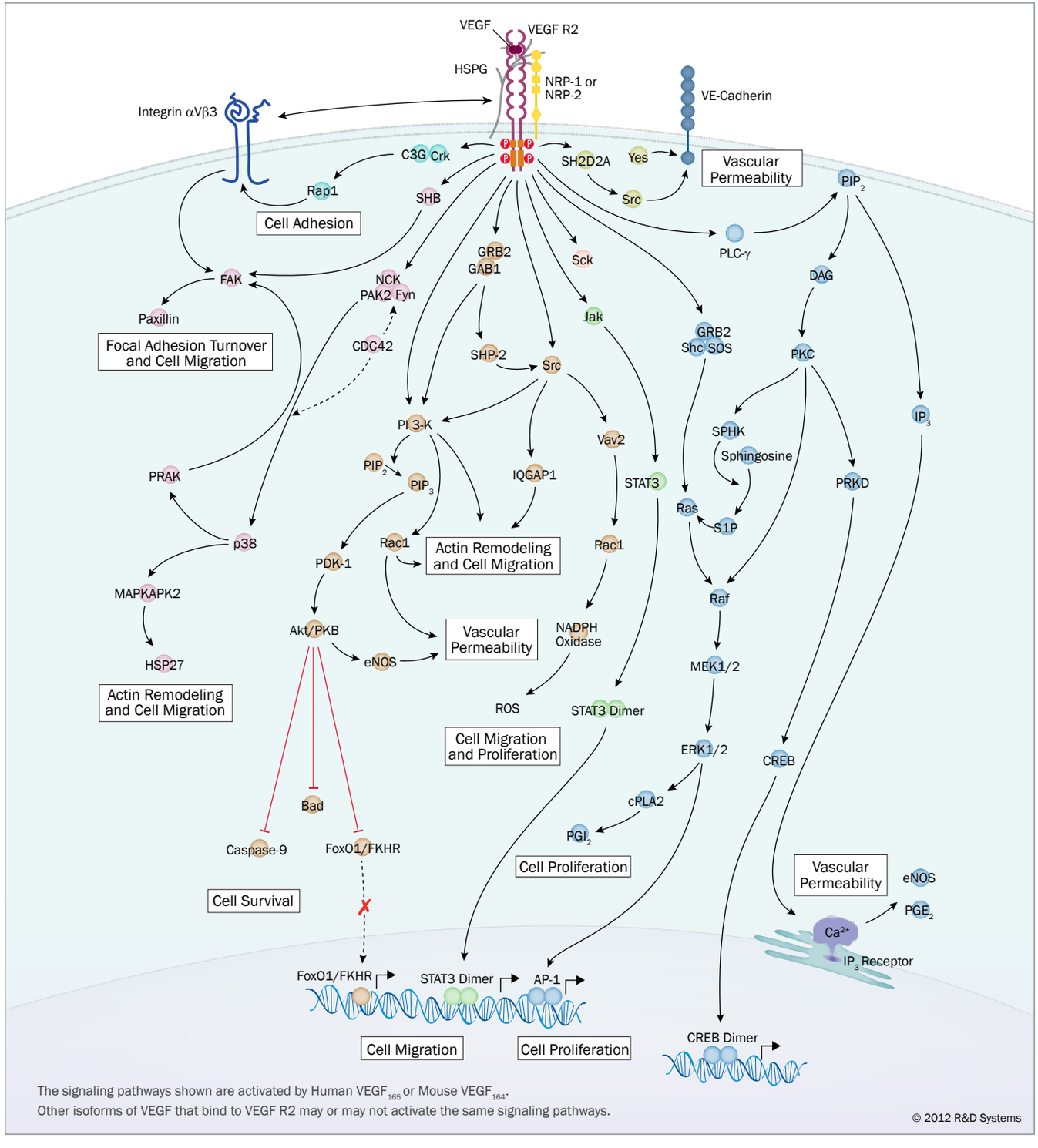
VEGF-VEGF R2 Signaling Pathways

Vascular Endothelial Growth Factor (VEGF) family members are potent mitogenic and angiogenic proteins with critical physiological roles in development and wound healing. In addition, they are also centrally involved in promoting tumor growth and vascular disease. Members of the VEGF gene family include VEGF/VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and Placental Growth Factor (PlGF). Alternative splicing of VEGF, VEGF-B, and PlGF can generate multiple isoforms with different biological properties. These isoforms include $VEGF_{110}$, $VEGF_{121}$, $VEGF_{145}$, $VEGF_{148}$, $VEGF_{162}$, $VEGF_{165}$, $VEGF_{165b}$, $VEGF_{183}$, $VEGF_{189}$, $VEGF_{206}$, $VEGF\text{-}B_{167}$, $VEGF\text{-}B_{187}$, PlGF-1, PlGF-2, PlGF-3, and PlGF-4. VEGFs homodimerize and transduce intracellular signals by binding to VEGF receptors (VEGF R1, VEGF R2, and VEGF R3), which are localized to the cell surface and have a unique specificity for different VEGF isoforms. VEGF binding and receptor activation is further modulated by co-receptors such as neuropilins and heparin sulfate proteoglycans (HSPGs). VEGF binding to its receptor promotes receptor dimerization, autophosphorylation, and activation of multiple downstream signaling cascades that stimulate vascular permeability, cell survival, proliferation, migration, or adhesion.



The signaling pathways shown are activated by Human $VEGF_{165}$ or Mouse $VEGF_{164}$.
Other isoforms of VEGF that bind to VEGF R2 may or may not activate the same signaling pathways.

Interact with this pathway | rndsystems.com/pathways_vegfr2signaling

April

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March

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Watson & Crick publish findings on the structure of DNA (1953)

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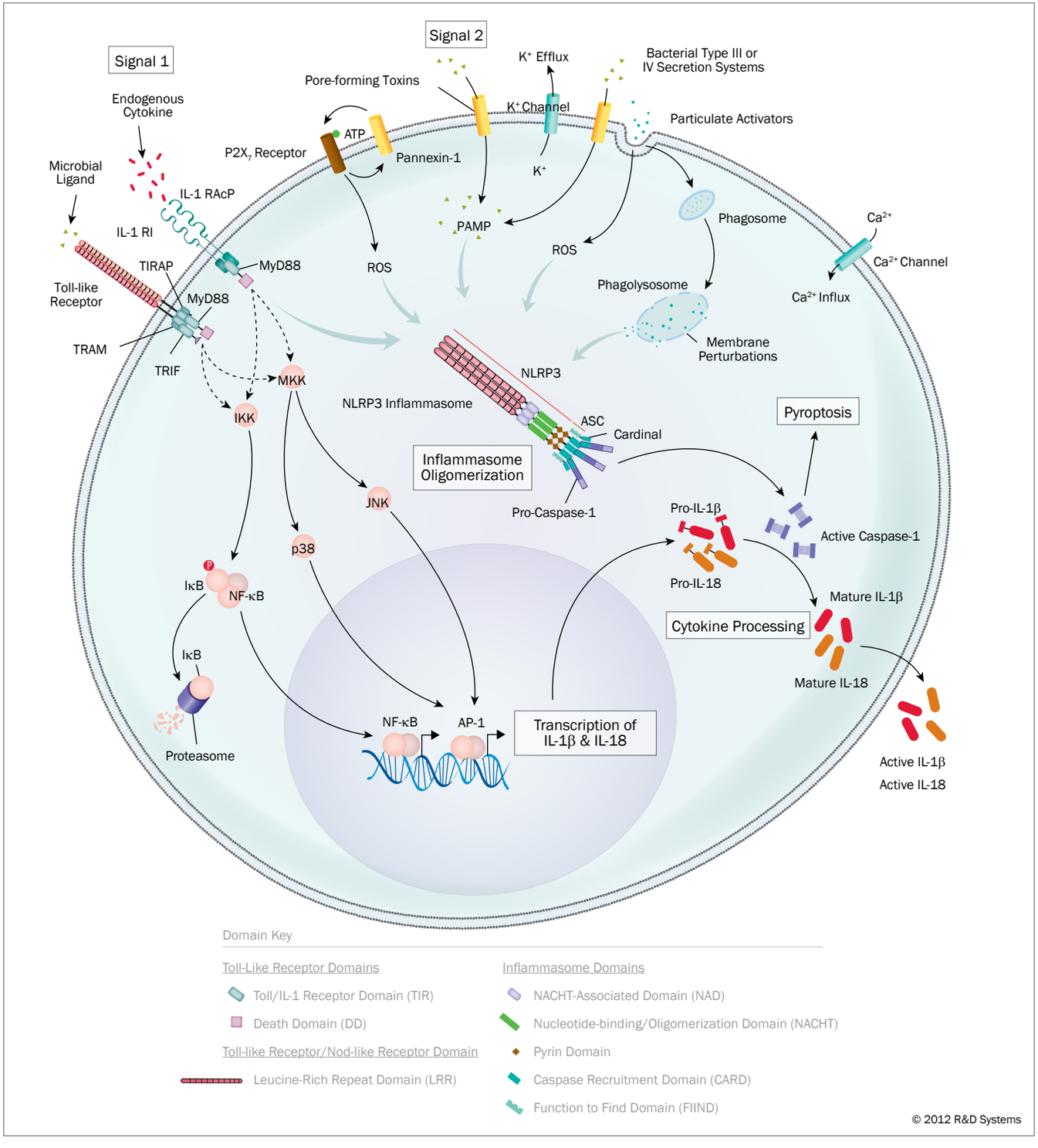
Inflammasome Activation Pathways

Nod-like receptors (NLRs) are a subset of cytoplasmic pattern recognition receptors that detect invading pathogens and initiate the innate immune response. NLRs are activated by pathogen-associated molecular patterns (PAMPs) or by damage-associated molecular patterns (DAMPs) exposed on the surface of, or released by damaged cells. Upon activation, some NLRs oligomerize to form multiprotein inflammasome complexes that serve as platforms for the recruitment, cleavage, and activation of inflammatory caspases. Inflammasome oligomerization requires two signals, a priming signal that results in the transcription of IL-1β and IL-18, and a second signal that promotes indirect activation of the inflammasome such as reactive oxygen species (ROS), ion or membrane perturbations, or extracellular ATP. Four inflammasome complexes (NLRP1, NLRP3, IPAF/NLRC4, and AIM2) have been partially characterized. These complexes contain a specific NLR family protein or AIM2, the ASC and/or Cardinal adaptor proteins, and Pro-Caspase-1. Inflammasome oligomerization induces the cleavage and activation of Caspase-1, which promotes the processing and secretion of IL-1β and IL-18, and may induce an inflammatory form of cell death known as pyroptosis. Secretion of IL-1β and IL-18 subsequently induces the expression of secondary pro-inflammatory mediators and promotes immune cell recruitment to the infection site. Although IL-1β and IL-18 have a beneficial role in promoting inflammation and eliminating infectious pathogens, mutations that result in constitutive inflammasome activation and the overproduction of IL-1β and IL-18 have been linked to autoinflammatory and autoimmune disorders.

Interact with this pathway | rndsystems.com/pathways_inflammasome



May

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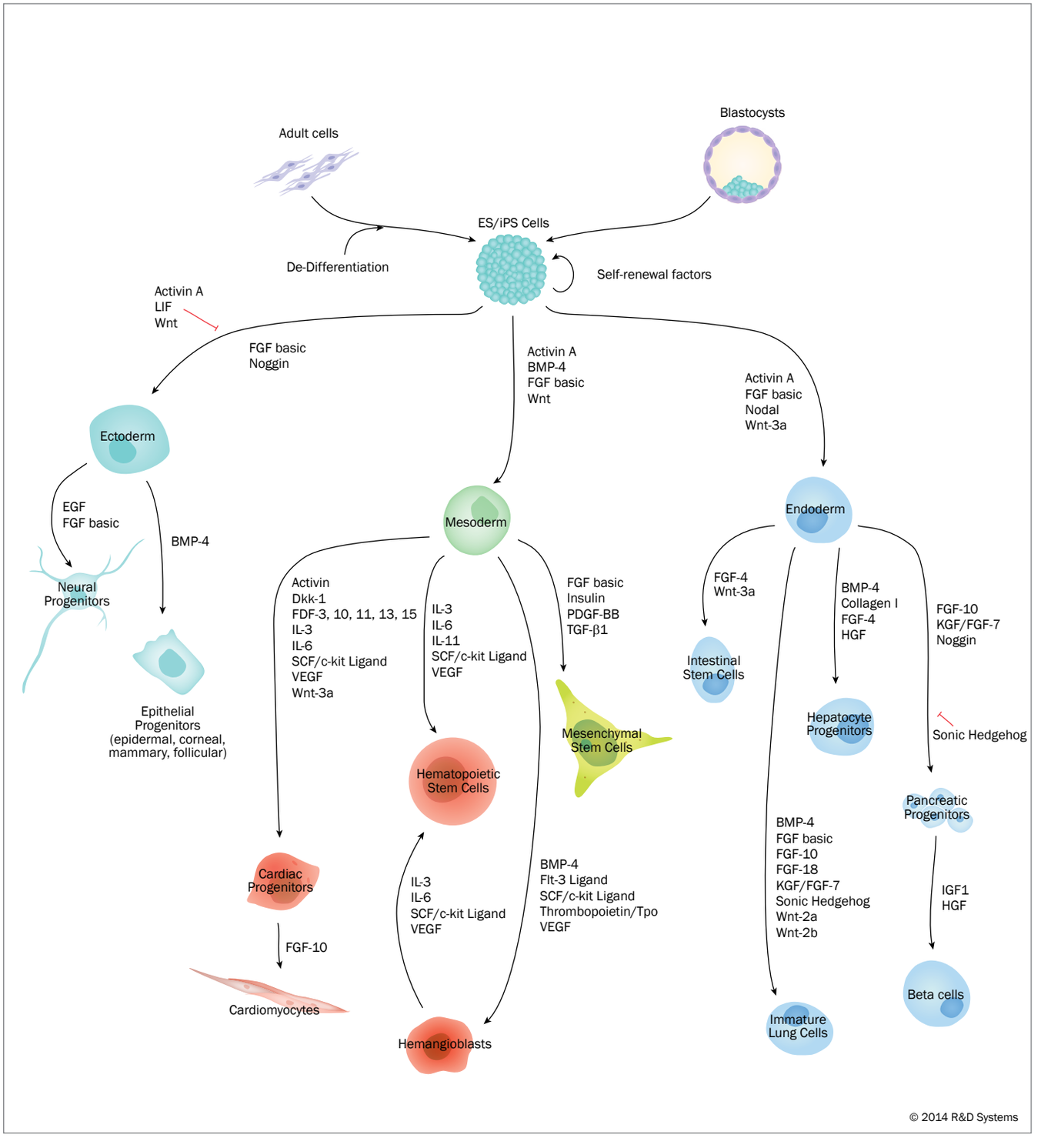
Embryonic and Induced Pluripotent Stem Cells & Lineage-specific Markers

Embryonic stem (ES) cells and induced pluripotent stem (iPS) cells are self-renewing progenitors that have the capacity to differentiate into cells of the ectoderm, mesoderm, and endoderm. Naturally existing ES cells can be isolated from the inner cell mass of a blastocyst while iPS cells are generated from terminally differentiated somatic cells through induced expression of specific transcription factors, including Oct-3/4, KLF4, SOX2, and c-Myc. Regardless of the source, pluripotent stem cells hold enormous potential in basic and clinical studies through their ability to differentiate into a wide variety of cell types, including neurons, pancreatic β cells, cardiomyocytes, and progenitor cells of the liver, lung and skin. The mechanisms controlling ES/iPS self-renewal and differentiation are influenced by a diverse set of growth factors, receptors, intracellular signaling molecules, and transcription factors. Cell fate determination often requires a tightly regulated temporal sequence of growth factor presentation and transcription factor expression. The factors shown in the graphic are known to influence ES/iPS pluripotency, proliferation, and lineage commitment. ES/iPS cells and their differentiated progeny can be identified by the expression of a unique combination of cell surface markers and transcription factors.

Interact with this pathway | rndsystems.com/pathways_esips



June

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May

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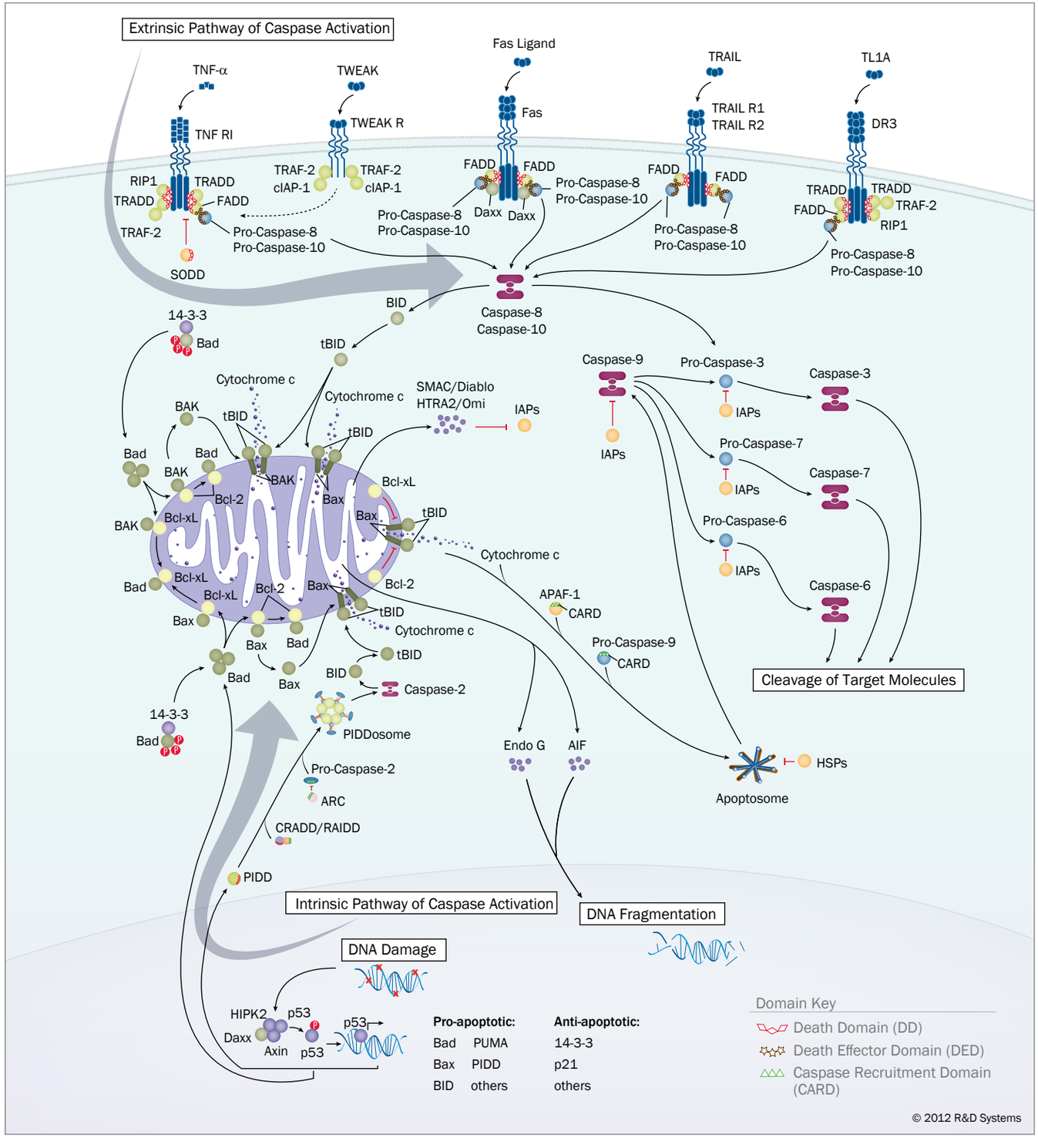
The Extrinsic and Intrinsic Pathways of Caspase Activation

Caspases are a family of aspartate-specific, cysteine proteases that serve as the primary mediators of apoptosis. All caspases are synthesized as inactive zymogens containing a variable length pro-domain, followed by a large (20 kDa) and a small subunit (10 kDa). Caspase activation occurs following receipt of an extrinsic or intrinsic death signal. The extrinsic pathway of caspase activation is initiated by ligand binding to cell surface death receptors, such as TNF RI, Fas/CD95, DR3, TRAIL R1/DR4, or TRAIL R2/DR5. These receptors oligomerize and associate with adaptor proteins that recruit Pro-Caspase-8 and Pro-Caspase-10, leading to their cleavage and activation. The intrinsic pathway of caspase activation is initiated by events such as DNA damage, growth factor withdrawal, or loss of contact with the extracellular matrix. These events ultimately lead to changes in the integrity of the mitochondrial membrane, which is regulated by Bcl-2 family proteins. Loss of mitochondrial integrity results in the release of pro-apoptotic proteins including Cytochrome c, which interacts with APAF-1 and Pro-Caspase-9 in the cytoplasm to form the apoptosome. Within this complex, Caspase-9 is processed and activated. Following DNA damage, the intrinsic pathway of caspase activation can also lead to formation of the PIDDosome and Caspase-2 activation. Once activated, initiator caspases cleave downstream effector caspases, which then promote the ordered disassembly of the cell by targeting a number of critical cellular proteins, including structural proteins, DNA repair proteins, and proteins involved in signal transduction pathways.

Interact with this pathway | rndsystems.com/pathways_apoptosissignaling



July

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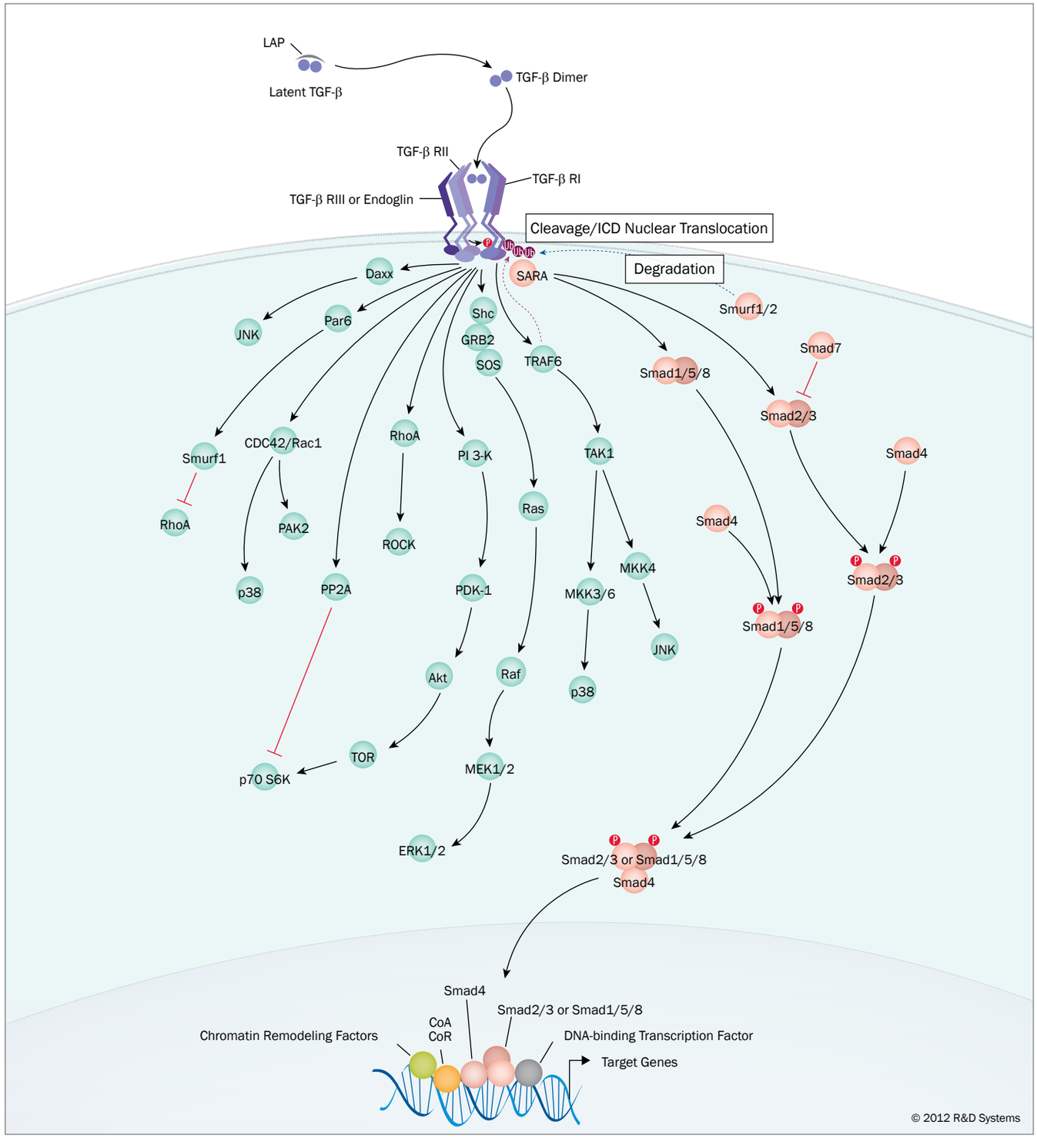
TGF-β Signaling Pathways

TGF-β proteins are highly pleiotropic cytokines that regulate a diverse range of processes during development and adult tissue homeostasis, including cell proliferation, apoptosis, autophagy, inflammation, angiogenesis, and epithelial-to-mesenchymal transition. TGF-β is normally secreted as part of an inactive, latent complex that consists of an N-terminal latency-associated peptide (LAP) and a C-terminal mature TGF-β monomer. Disulfide-linked homodimers of LAP and TGF-β remain noncovalently associated after secretion, forming the small latent TGF-β complex. Activation of TGF-β is controlled both spatially and temporally by the actions of proteases or select integrins.

TGF-β signals through a heterotetrameric receptor complex composed of two type I and two type II transmembrane receptor subunits. Following ligand binding, TGF-β RII phosphorylates TGF-β RI, leading to the recruitment and phosphorylation of Smad2 and Smad3 in most cell types. Alternatively, Smad1 and Smad5 can be activated by TGF-β signaling in some cell types depending on the type I receptor that is expressed. Activated Smad proteins associate with Smad4 and translocate to the nucleus, where they recruit additional transcriptional regulators that control the expression of numerous target genes. In addition, TGF-β can activate a number of Smad-independent signaling pathways, including Ras/MAPK, PI 3-K/Akt, p38, JNK, and RhoA/ROCK in a cell type-specific and context-dependent manner. Activation of these pathways may also contribute to the cellular responses induced by TGF-β.

Interact with this pathway | rndsystems.com/pathways_tgfbeta_signaling



August

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20	21	22	23	24	25 Dr. Yamanaka Publishes his paper on the discovery of iPSCs (2006)	26
27	28	29	30	31	September S M T W Th F S 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30	

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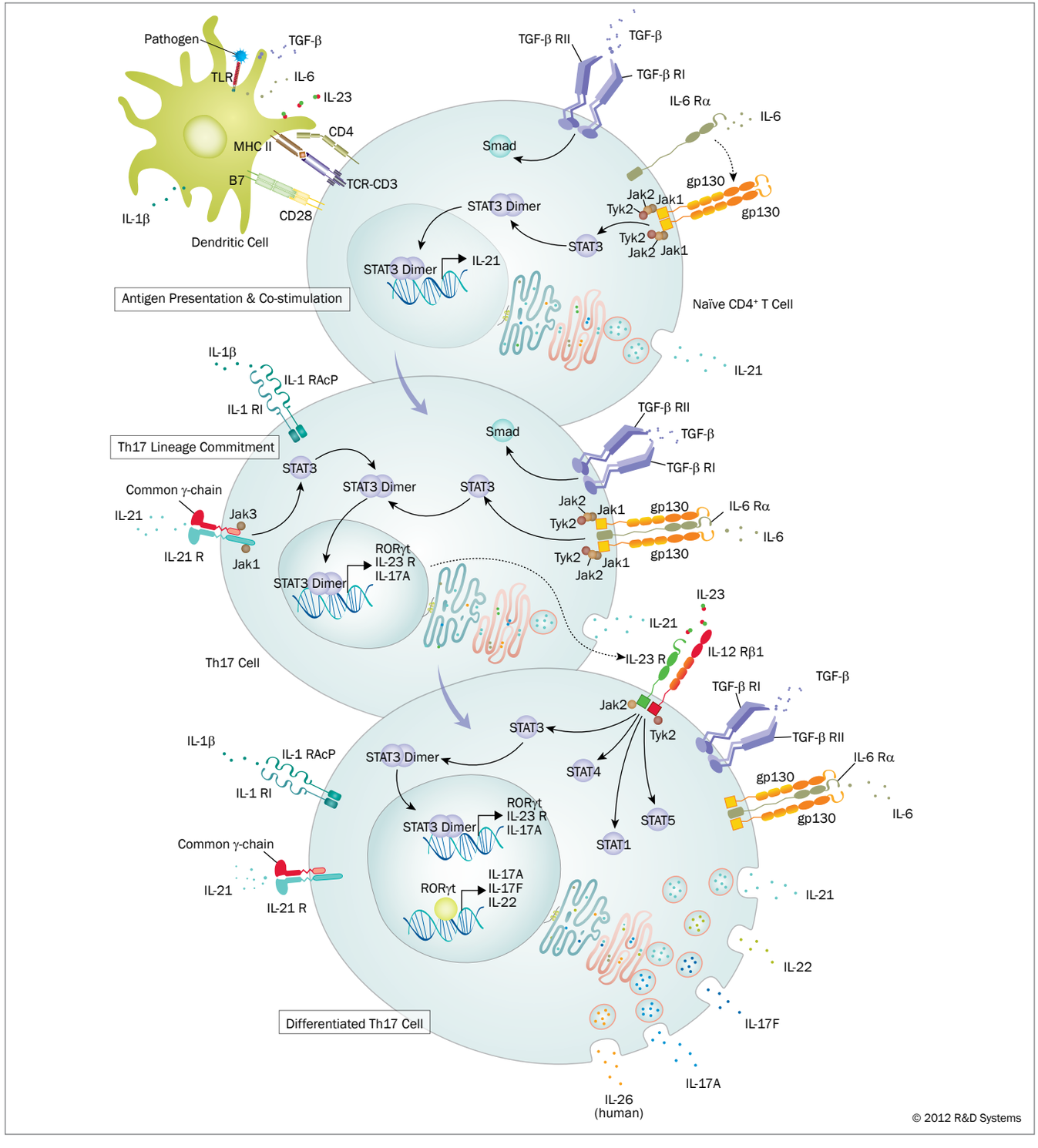
Th17 Differentiation Pathway

T helper type 17 (Th17) cells are involved in the immune response mounted against specific fungi and extracellular bacteria. In mice, Th17 cells develop from naive CD4$^+$ T cells in the presence of TGF-β and IL-6. These cytokines induce the STAT3-dependent expression of IL-21, IL-23 R, and the transcription factor, RORγt. IL-21 and IL-23 regulate the establishment and clonal expansion of Th17 cells, while RORγt-induced gene expression leads to the secretion of IL-17A, IL-17F, and IL-22. Cytokines secreted by Th17 cells stimulate chemokine secretion by resident cells, leading to the recruitment of neutrophils and macrophages to the site of inflammation. These cells, in turn, produce additional cytokines and proteases that further exacerbate the immune response. In contrast to mouse Th17 differentiation, Th17 polarization in humans requires IL-1β, IL-6, IL-21, and IL-23, but seems to be less dependent upon TGF-β. One other notable difference is that in addition to IL-17A, IL-17F, and IL-22, human Th17 cells secrete IL-26, an IL-10 family cytokine without a murine homologue. Cytokines produced by Th17 cells can have both beneficial and pathogenic effects. While they play a central role in eliminating harmful microbes, persistent secretion of Th17 cytokines promotes chronic inflammation and may be involved in the pathogenesis of inflammatory and autoimmune diseases, including rheumatoid arthritis, multiple sclerosis, and inflammatory bowel disorders.

Interact with this pathway | rndsystems.com/pathways_th17diff



September

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28

Alexander Flemming discovers Penicillin in 1928

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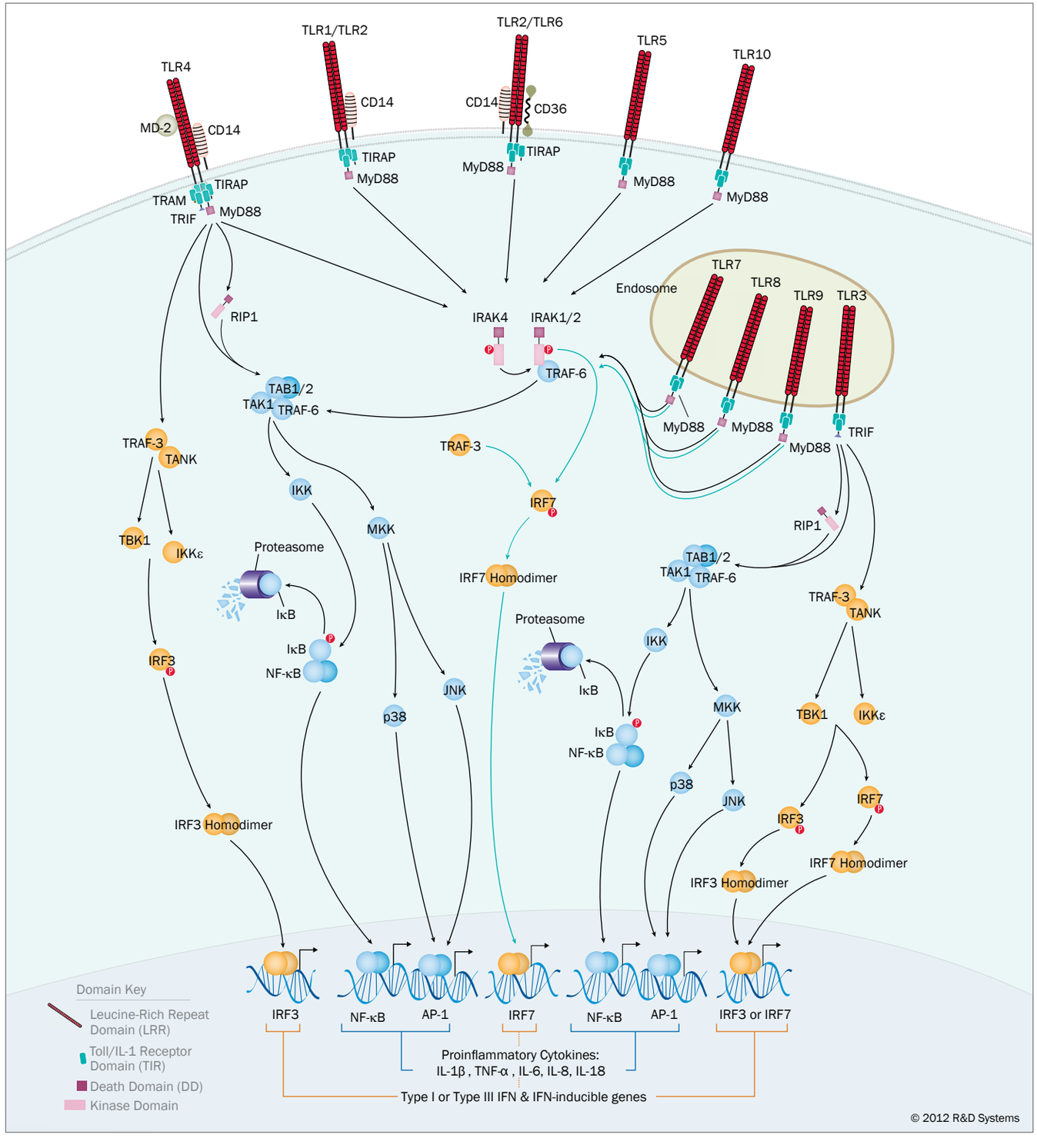
Toll-Like Receptor Signaling Pathways

Toll-like receptors are a family of type I transmembrane pattern recognition receptors (PRRs) that sense invading pathogens or endogenous damage signals and initiate the innate and adaptive immune response. There are ten functional TLRs in humans (TLR1–10) and twelve in mice (TLR1–9, 11–13). Various combinations of these receptors are expressed by different subsets of immune and non-immune cell types including monocytes, macrophages, dendritic cells, neutrophils, B cells, T cells, fibroblasts, endothelial cells, and epithelial cells. Of the human TLRs, TLR1, 2, 4, 5, 6, and 10 are expressed on the cell surface and primarily recognize microbial membrane and/or cell wall components, while TLR3, 7, 8, and 9 are expressed in the membranes of endolysosomal compartments and recognize nucleic acids. TLRs have a variable number of ligand-sensing, leucine-rich repeats (LRR) at their N-terminal ends and a cytoplasmic Toll/IL-1 R (TIR) domain. The TIR domain mediates interactions between TLRs and adaptor proteins involved in regulating TLR signaling including MyD88, TRIF, TRAM, and TIRAP/MAL. Signaling pathways activated downstream of these adaptor molecules promote the NF-κB- and AP-1-dependent expression of pro-inflammatory cytokines and chemokines, and the IRF3-/IRF7-dependent expression of type I and type III interferons. As a result, additional immune cells are recruited to the infection site and the pathogenic microbes and infected cells are eliminated. Although TLRs provide protection against a wide variety of pathogens, inappropriate or unregulated activation of TLR signaling can lead to chronic inflammatory and autoimmune disorders.

Interact with this pathway | rndsystems.com/pathways_tlrsignaling



October

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22 Edison tests first commerically viable electric light bulb in 1879	23	24	25	26	27	28
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September

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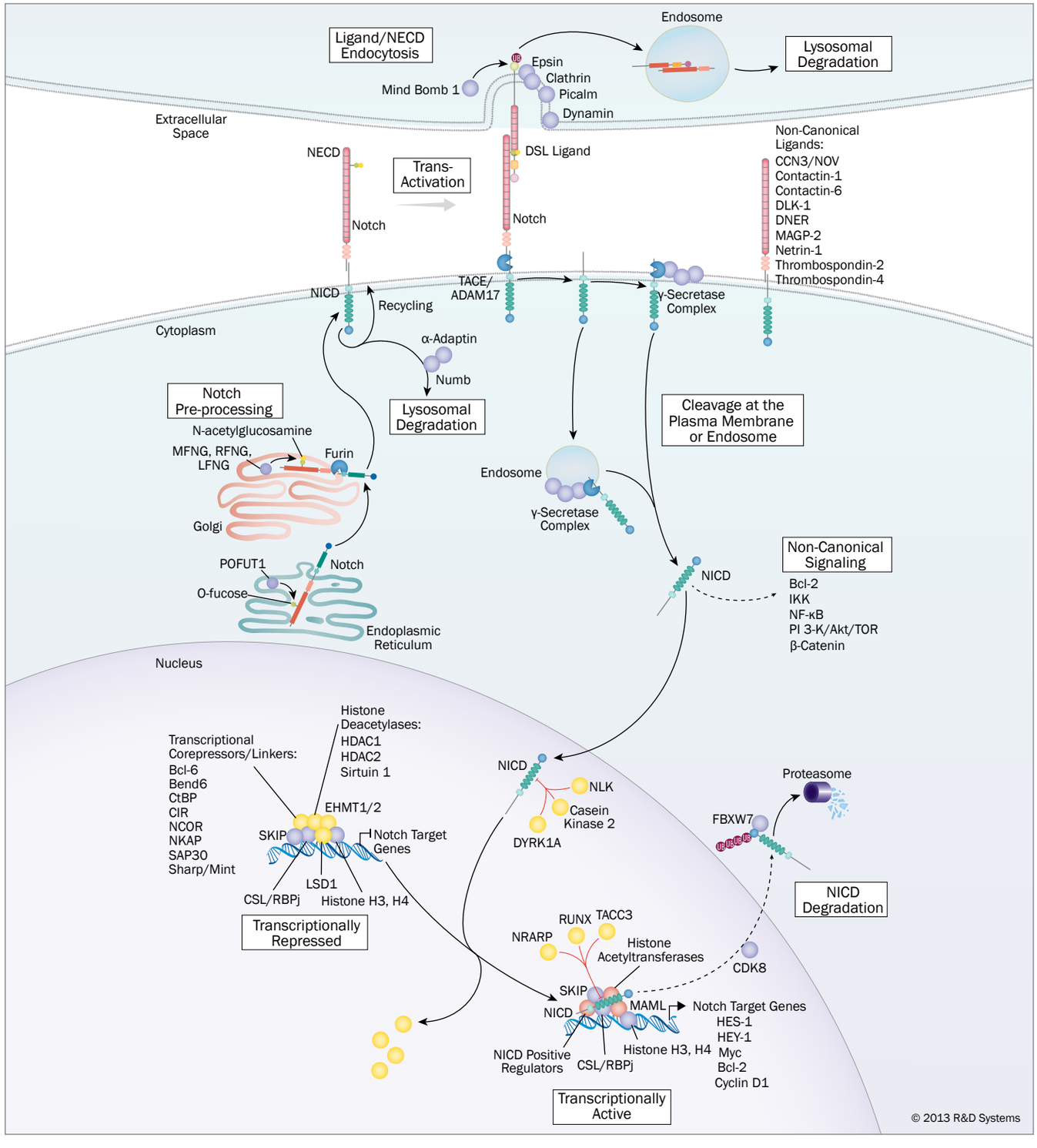
Notch Signaling Pathways

The Notch pathway is highly conserved and has a wide range of physiological roles including regulating cell fate, proliferation, angiogenesis, cell survival, and the immune response. Aberrant Notch activity may also have complex and context-dependent effects on tumorigenesis. Notch receptors (Notch-1, -2, -3, -4) and ligands exist as type I transmembrane proteins. In mammals, canonical Notch ligands include members of the Delta-like (DLL) and Jagged families. Upon ligand binding, the Notch receptor is proteolytically cleaved in a stepwise manner, releasing the Notch intracellular domain (NICD) into the cytosol where it translocates to the nucleus. In the absence of the NICD, the DNA binding protein CSL/RBPj acts as a transcriptional repressor in complex with a range of putative co-repressors, linker proteins, and enzymes. In the nucleus, the NICD binds CSL/RBPj and Mastermind-like (MAML), recruiting transcriptional co-activators and forming a complex that induces the transcription of Notch target genes. The activity and turnover of the NICD may be regulated by ubiquitination and phosphorylation. It is the balance between the activities of the opposing regulators that dictate the level of overall Notch activity. Adding to the complexity of the Notch pathway, it is becoming increasingly evident that Notch can signal via non-canonical means. For instance non-canonical ligands have been identified that may activate or suppress Notch signaling depending on the context. There is also crosstalk between Notch and other signaling pathways and molecules, including Akt/TOR, NF-κB, β-Catenin, and others.

Interact with this pathway | rndsystems.com/pathways_notch



November

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
October / December			1	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24 Darwin's *Origin of Species* is published	25
26	27	28	29	30		

October

S	M	T	W	Th	F	S
1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31				

December

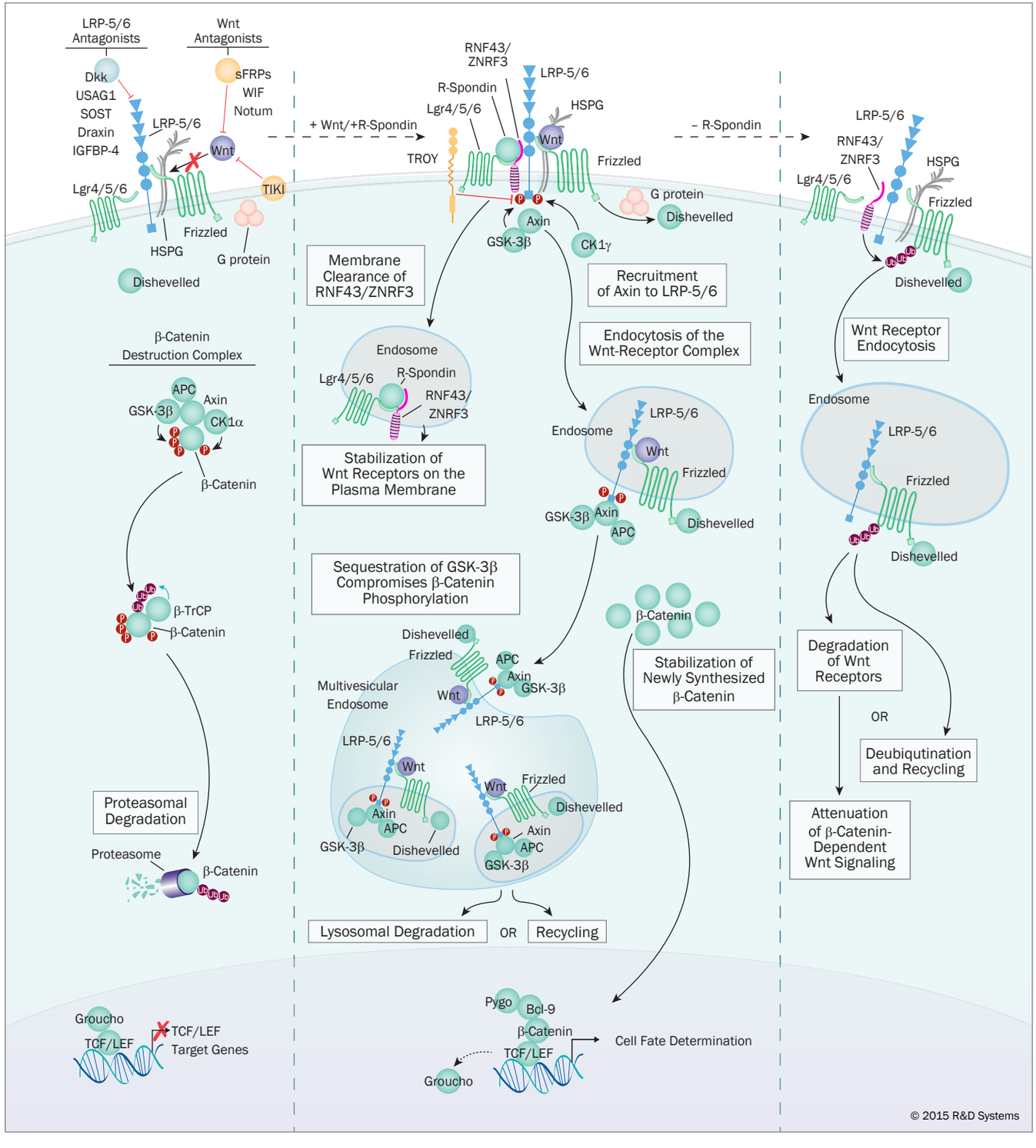
S	M	T	W	Th	F	S
					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17	18	19	20	21	22	23
24 31	25	26	27	28	29	30

bio-techne®

β-Catenin-dependent Wnt Signaling Pathway

Wnts are a large family of secreted glycoproteins that play a central role in embryonic development, differentiation, cell motility, proliferation, and adult tissue homeostasis. Wnt signaling can activate β-Catenin-dependent transcription and at least two well-characterized β-Catenin-independent pathways, the planar cell polarity (PCP) pathway and the Wnt/Ca^{2+} pathway. The β-Catenin-dependent signaling pathway is initiated by Wnt binding to the Frizzled and LRP-5/6 receptors. This binding activates Dishevelled, which subsequently recruits the Axin protein complex (Axin, APC, CK1, GSK-3β) to the receptor. GSK-3β and CK1 phosphorylate LRP-5/6, leading to internalization of the Wnt-receptor complex in endosomes that give rise to multivesicular bodies. Sequestration of GSK-3β in multivesicular bodies compromises its ability to phosphorylate newly synthesized β-Catenin. Unphosphorylated β-Catenin accumulates and translocates to the nucleus, where it associates with TCF/LEF transcription factors and co-activators to induce the expression of Wnt target genes. In the absence of Wnt, cytoplasmic β-Catenin is phosphorylated by CK1 and GSK-3β, creating a docking site for β-TrCP, an E3 ubiquitin ligase that promotes its ubiquitination and proteasomal degradation. β-Catenin-dependent Wnt signaling is enhanced by R-Spondins, which bind to the leucine-rich, G protein-coupled receptors, Lgr4, 5, or 6 and RNF43/ZNRF3, a transmembrane E3 ubiquitin ligase that acts on Frizzled receptors. Binding of R-Spondins to Lgr and RNF43/ZNRF3, leads to endocytosis of the complex, stabilizing Wnt receptors and enhancing Wnt responsiveness.

Interact with this pathway | rndsystems.com/pathways_wntsignaling



December

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
November S M T W Th F S 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 January 2018 S M T W Th F S 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31					1	2
3	4	5	6	7	8	9
10	11	12	13	14	15	16
17 Wright Brother's Day First successful flight near Kitty Hawk, NC in 1903	18	19	20	21	22	23
24 31	25	26	27	28	29	30

2017 Holidays

January

1 New Year's Day
4 Myanmar Independence Day
7 Orthodox Christmas Day
14 Orthodox New Year's Day
16 Martin Luther King Jr. Day
27 International Holocaust Rememberance Day
28 Chinese New Year

February

2 Groundhog Day
3 National Wear Red Day
3 Setsubun-sai (Shinto)
4 World Cancer Day
5 Superbowl Sunday
11 Magha Puja (Buddhist)
14 Valentine's Day
20 President's Day
27 Great Lent begins (Orthodox)
28 Mardi Gras

March

1 Ash Wednesday
8 International Women's Day
11 Purim
12 Daylight Savings Time Starts (US)
14 Albert Einstein's Birthday
17 St. Patrick's Day
20 International Day of Happiness
20 March Equinox
20 Vernal Equinox (Northern Hemisphere)
20 Naw-Ruz
22 World Water Day
26 Mother's Day (UK & Ireland)

April

1 April Fool's Day
2 World Autism Awareness Day
7 World Health Day
9 Palm Sunday
9 Mahavir Jayanti
10 Erev Pesach
11 First night of Passover
14 Good Friday
14 Baisakhi
16 Easter Sunday
16 Pascha (Easter - Orthodox)
17 US Tax Day
22 Earth Day
24 Isra and Mi'raj (Islam)
25 World Malaria Day

May

5 Cinco De Mayo
10 Vesak
14 Mother's Day
15 International Day of Families
20 Armed Forces Day
25 Ascension (Orthodox)
27 Start of Ramadan
29 Memorial Day

June

4 Pentecost
14 Flag Day (US)
18 Father's Day
20 First Day of Summer
21 Summer Solstice (Northern Hemisphere)
25 Eid al-Fitr (Islam)

July

4 Independence Day (US)
15 Asalha Puja

August

15 Obon
15 Krishna Janmashtami
18 Paryushana-Parva

September

1 Eid al-Adha
4 Labor Day (US)
1 Rosh Hashanah
22 Autumn Equinox (Northern Hemisphere)
30 Dasara
30 Yom Kippur

October

6 Sukkot
9 Native American Day (US)
9 Columbus Day (US)
9 Thanksgiving Day (Canada)
12 Sichat Torrah begins
19 Diwali Begins
31 Halloween

November

5 Daylight Savings Time Ends (US)
11 Veteran's Day (US)
11 Rememberance Day
23 Thanksgiving Day (US)

December

6 Saint Nicholas' Day
12 First Night of Chanukah
20 Final Night of Chanukah
21 Winter Solstice
25 Christmas Day
26 Boxing Day
31 New Year's Eve
Dec. 26–Jan. 1, 2018 Observance of Kwanzaa

2017 Bio-Techne Events

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Meeting	Date
AACR Annual Meeting, Washington D.C.	April 1–5, 2017
ISSCR Annual Meeting, Boston, MA	June 14–17, 2017
Society for Neuroscience Annual Meeting, Washington D.C.	November 11–15, 2017

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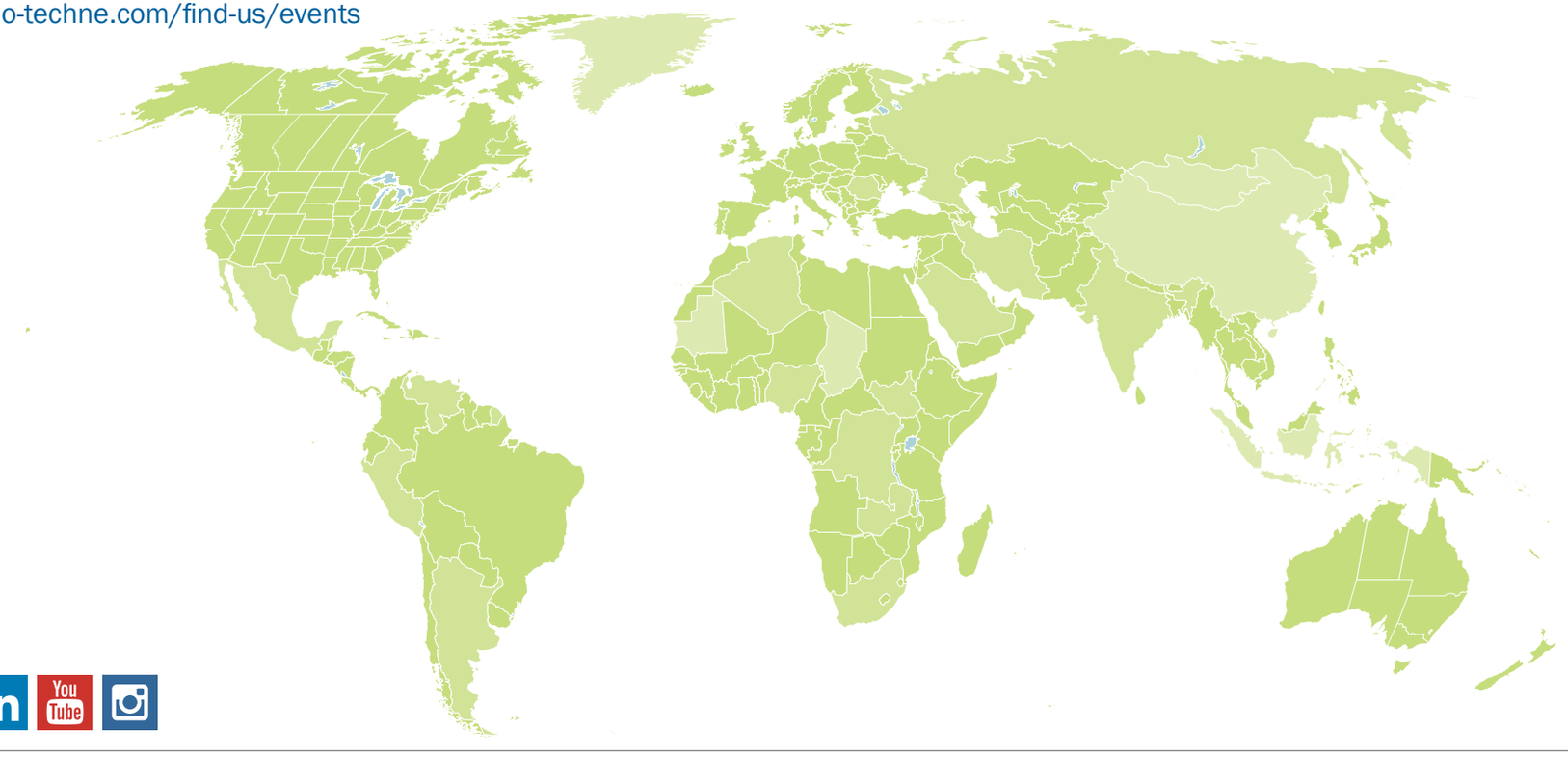

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