

Angiogenesis and Cardiovascular Development

from Cell Signaling Technology

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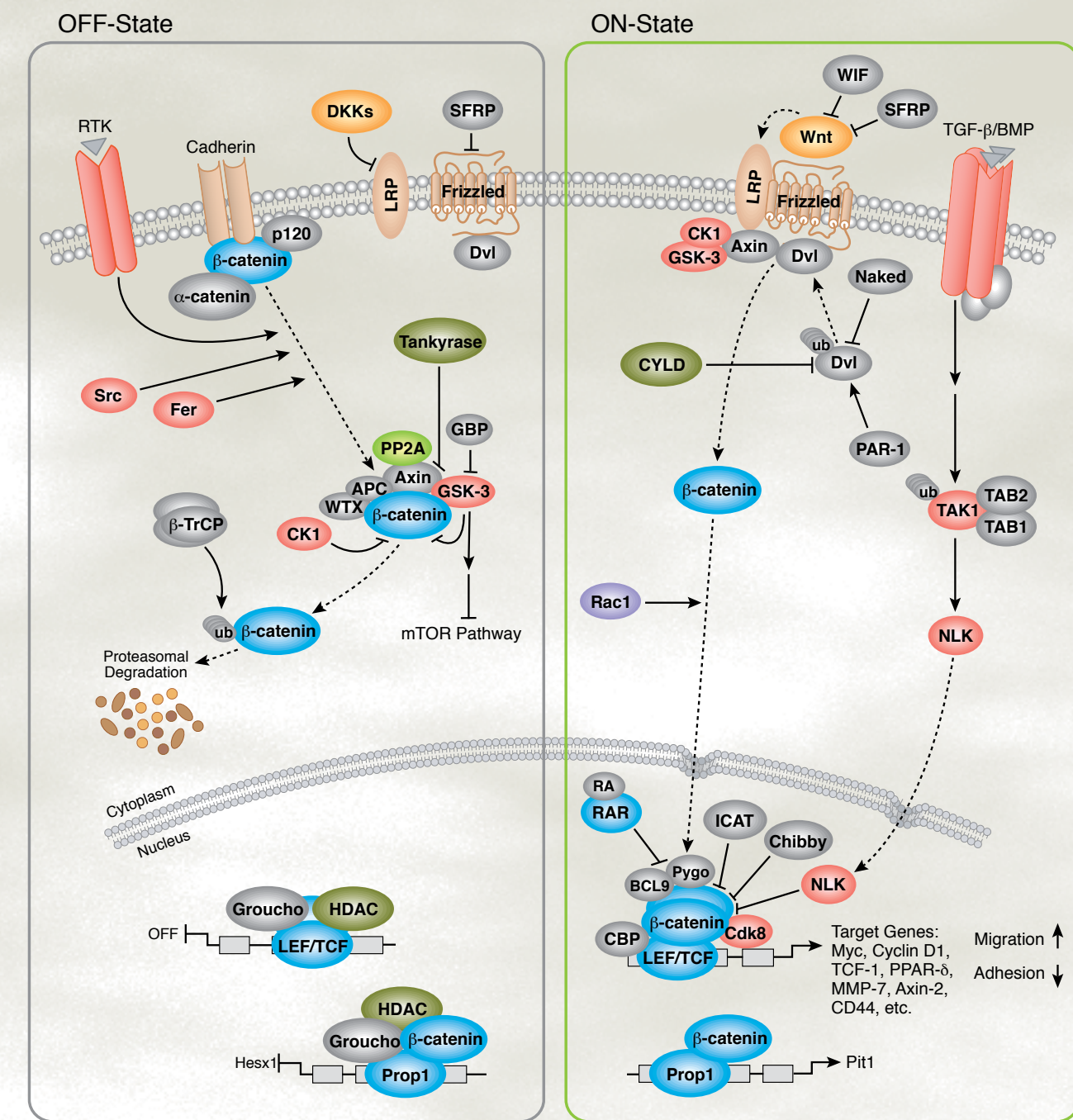
As a company driven by science, our goal is to accelerate biomedical research by developing a "research tool box" that enables researchers to monitor and measure protein activity. We strive to meet contemporary and future research challenges by creating the highest quality, most specific, and thoroughly validated antibodies and related reagents.

As a committed member of the research community, we practice responsible and sustainable business methods and invest heavily in research and development. We also encourage thoughtful use of our limited natural resources by highlighting environmental issues in our catalog and by promoting conservation and recycling.

All pathways were created by research scientists at Cell Signaling Technology and reviewed by leading scientists in the field. Visit www.cellsignal.com for additional reference materials and comprehensive validation data for over 4,000 antibodies and related reagents.

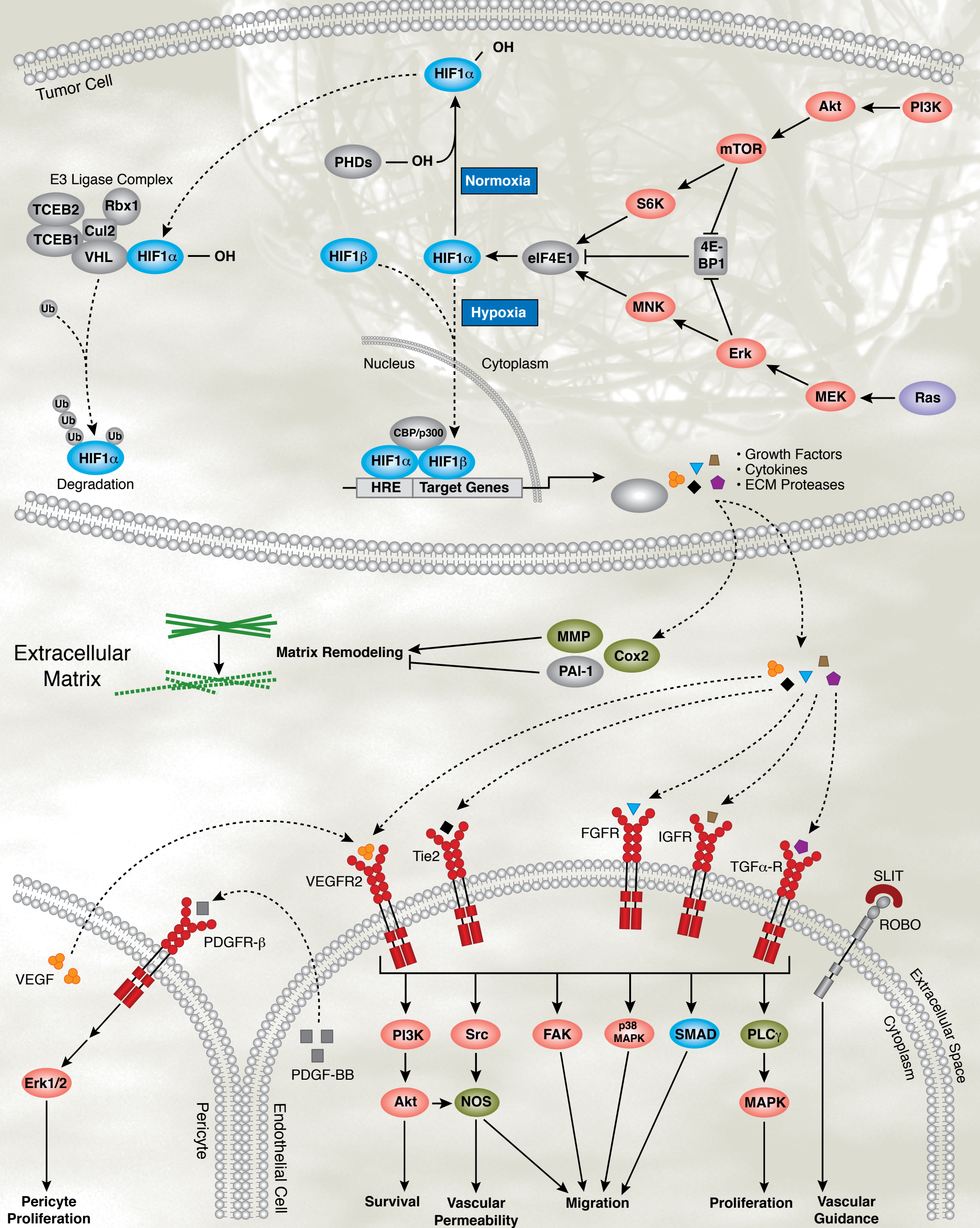
Wnt/ β -Catenin Signaling

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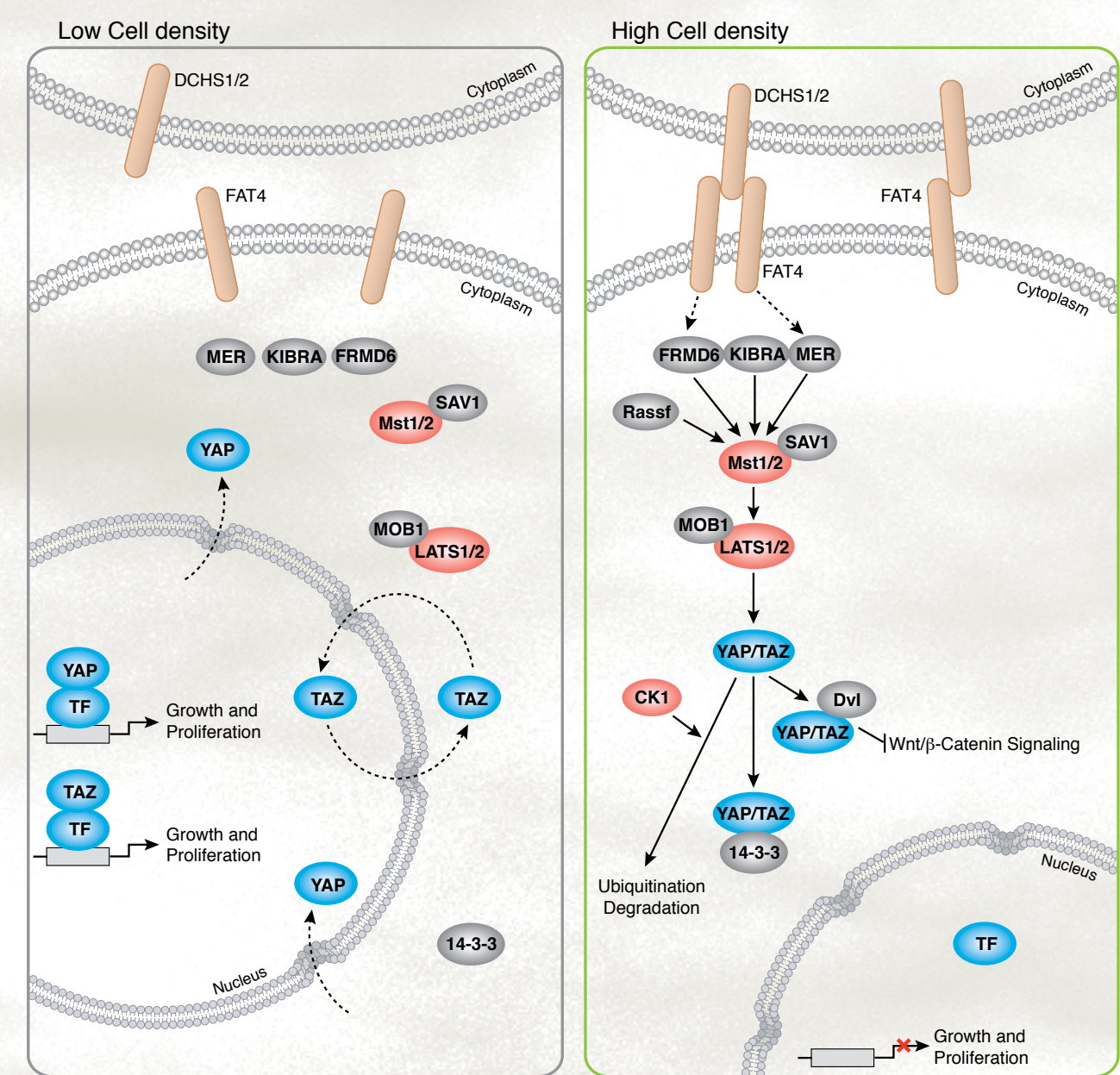
Angiogenesis

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Hippo Signaling

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Transcription Factors (TF) include: TEAD, TEF, RunX1, RunX2, p73, PPAR γ , and others

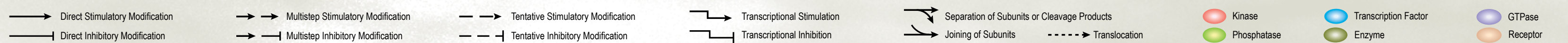
Angiogenesis

Pathway Description: Angiogenesis results in the formation of new blood vessels and can be induced by tumor growth, tissue wound, and inflammation. Rapid tumor cell growth creates intracellular hypoxia. Hypoxia-inducible factor (HIF) is a transcription factor that responds to changing intracellular oxygen concentration. Under typical oxygen levels (normoxia), HIF is hydroxylated and acetylated, modifications that target the transcription factor for VHL-mediated ubiquitin degradation. During hypoxia, HIF accumulates and is transported to the nucleus where it induces expression of numerous target gene products. Secreted growth factors (such as VEGF, FGF, and TGF) induce signaling pathways (including PLC γ , PI3K, Src, Smad signaling) that result in endothelial cell proliferation, increased vascular permeability, and cell migration. In addition to hypoxia, PI3K and Ras pathways can increase HIF expression by promoting HIF translation.

Pericytes are support cells that provide structural support for newly formed blood vessels, promote endothelial cell survival, guide sprouting vessels, and regulate vasoconstriction and dilation. This is done through a reciprocal signaling mechanism in which PDGF-BB secreted into the matrix by endothelial cells acts as a ligand for PDGF receptor- β located on the pericyte membrane. In return, pericytes produce and secrete VEGF that signals through the endothelial VEGF receptor.

Extracellular matrix proteases and regulators induce tissue matrix remodeling in preparation for migration of endothelial cells from existing vessels to form new tubing. Tissue wounding, ischemia, or inflammation recruit macrophages and bone marrow-derived inflammatory cells (BDMC) to wound areas, and secrete a similar panel of proteins to induce angiogenesis.

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Wnt/ β -Catenin Signaling

Pathway Description: The Wnt/ β -catenin pathway regulates cell fate decisions during development of vertebrates and invertebrates. The Wnt ligand is a secreted glycoprotein that binds to Frizzled receptors, which triggers a cascade resulting in displacement of the multifunctional kinase GSK-3 β from the APC/Axin/GSK-3 β complex. In the absence of Wnt-signal (Off-state), β -catenin, an integral cell-cell adhesion adaptor protein as well as transcriptional co-regulator, is targeted for degradation by the APC/Axin/GSK-3 β complex. Appropriate phosphorylation of β -catenin by coordinated action of CK1 and GSK-3 β leads to its ubiquitination and proteasomal degradation through the β -TRCP/SKP complex. In the presence of Wnt binding (On-state), Dishevelled (Dvl) is activated by phosphorylation and poly-ubiquitination, which in turn recruits GSK-3 β away from the degradation complex. This allows for stabilization of β -catenin levels, Rac1-dependent nuclear translocation, and recruitment to the Lef/TCF

DNA-binding factors where it acts as an activator for transcription by displacement of Groucho-HDAC co-repressors. Additionally, in complex with the homeodomain factor Prop1, β -catenin has also been shown to act in context-dependent activation as well as repression complexes. Importantly, point-mutations in β -catenin lead to its deregulated stabilization. APC and Axin mutations also have been documented in some tumors, underscoring the deregulation of this pathway in human cancer. During development, the Wnt/ β -catenin pathway integrates signals from many other pathways including retinoic acid, FGF, TGF- β , and BMP in many different cell-types and tissues. In addition, GSK-3 β is also involved in glycogen metabolism and other key pathways, which has made its inhibition relevant to diabetes and neurodegenerative disorders.

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Hippo Signaling

Pathway Description: Hippo signaling is an evolutionarily conserved pathway that controls cell proliferation, apoptosis, and organ size in response to changing cell density levels. At relative low cell density, transcription co-activators YAP and TAZ bind transcription factors to induce expression of genes that favor cell growth and proliferation. Transcription factors activated following interaction with YAP and/or TAZ include TEAD, Runx2, p73, and TBX5. Interaction with p73 follows DNA damage and may promote apoptosis; most other activated transcription factors likely activate transcription of genes favoring cell growth and proliferation. As cell density increases, interaction between membrane-bound upstream hippo pathway regulators trigger activation of cytoplasmic kinases Mst1/2 and LATS1/2. Activated Mst kinase (the eponymous Hippo in Drosophila) associates with

the adaptor WW45 and activates the downstream LATS kinase, which phosphorylates YAP and TAZ. Phosphorylation of these co-activators allows binding of the cytoplasmic anchor 14-3-3 protein. Prevented from entering the nucleus, YAP and TAZ can no longer help promote transcription of genes that favor increased cell growth and proliferation. Several parts of the pathway in mammalian cells remain unclear, but are suggested by better-characterized Drosophila counterparts. Cell surface protein interactions may involve Dachsous and Fat cadherins; the mechanism of Mst activation by upstream regulators Merlin and FRMD6 (Expanded in Drosophila) also remains unclear. Kinases PKA and PAK may inhibit Merlin while activated Fat receptor may inhibit cytoplasmic Dachsous.

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