INGENUITY PATHWAY ANALYSIS

Canonical Pathway

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Canonical Pathway: eNOS Signaling

Description: Nitric oxide (NO) is a short-lived free radical involved in diverse physiological and pathological processes. It is produced along with L-Citrulline by the oxidation of L-Arginine. This reaction can be catalyzed by three different isoforms of NOS. Type-I (nNOS) and Type-III (eNOS) are constitutively expressed as latent enzymes and require a higher concentration of Ca2+ for their enzyme activity. In contrast, Type-II (iNOS) is Ca2+-independent. NO production by endothelial cells is stimulated by a variety of mechanical forces such as shear stress and cyclic strain, and humoral factors ranging from growth factors to peptide hormones. eNOS is a dually acylated peripheral membrane protein that is targeted to endothelial plasmalemmal caveolae through an interaction with the protein CAV1. CAV1 inhibition of eNOS is relieved by CALM, which causes dissociation of eNOS from CAV1. This regulatory mechanism is further modified by HSP90, which binds to eNOS and facilitates displacement of CAV1 by CALM.

Physiologically, endothelial cells are exposed to the hemodynamic forces of blood including laminar shear stress. Shear stress via G-proteins activates several signal transduction pathways, including PI3K, PDK and AC via cAMP, leading to eNOS activation by phosphorylation of serine residues. Additional stimuli, such as VEGF, estrogen, S-1P and BDK, bind to their cognate receptors and stimulate PI3K/AKT. VEGF and Acetylcholine also activate PLCγ. Metabolic stress triggers the breakdown of ATP which stimulates AMPK to phosphorylate eNOS on Serine 1179. Other proteins which are associated with increased eNOS activity or NO release are DNM2 and Porin, which colocalize and directly interact with eNOS. An efficient supply of substrate is ensured by localization of the arginine transporter CAT1 in caveolae and its direct interaction with eNOS.

Myristoylation of eNOS occurs co-translationally and targets eNOS to cellular membranes where eNOS is then palmitoylated. These lipid modification events promote eNOS association with cell membranes and are essential for linking upstream signal transduction pathways to eNOS activity in cells. CHIP interacts with both HSP70 and HSP90 and negatively regulates eNOS trafficking into the Golgi complex. By contrast, NOSIP and NOSTRIN negatively regulate eNOS localization in the plasma membrane. eNOS plays a crucial role in the state of blood vessel vasodilation and hence blood pressure regulation. Abnormalities in vascular NO production are thought to contribute to the pathogenesis of certain vascular disorders such as those of atherosclerosis and hypertension.

Signaling Pathway Categories: Cardiovascular Signaling

Top Functions & Diseases: Cell Death and Survival; Skeletal and Muscular Disorders; Skeletal and Muscular System Development and Function

Molecules: 1-phosphatidyl-D-myo-inositol 4,5-bisphosphate, acetylcholine, AChR, ADCY, Akt, AMPK, apoptosis, AQUAPORIN, ATP, BDKR, Ca2+, Calmodulin, CASP3, CASP8, CASP9, CAV1, citrulline, Cng Channel, cyclic AMP, cyclic GMP, Cyclin A, diacylglycerol, DNM2, estrogen, estrogen receptor, GNAQ, GNAS, GTP, Hsp70, Hsp90, inositol triphosphate, ITPR, KNG1, L-arginine, Lpa receptor, nitric oxide, NOS3, NOSIP, NOSTRIN, PDPK1, PI3K (complex), Pka, Pkc(s), PLC gamma, PRKG1, proliferation of cells, sGC, SLC7A1, sphingosine-1-phosphate, STUB1, vasodilation

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Drug Summary - Overview of drugs targeting molecules in Canonical Pathway

Showing 3 of 432 row(s) of Drug data.

Drug Name	Targets	Actions	Brand Names	Indications/Status
17-alpha-ethinylestradiol	ESR1	agonist	Amenoron, Amenorone, Cyclosa, Dicromil, Diognat-E, Diogyn E, Diogyn-E, Diprol, Dyloform, Ertonyl, Esteed, Estigyn, Estinyl, Eston-E, Estopherol, Estoral, Estorals, Ethidol, Ethinoral, Ethinyl-Oestradiol Effik, Ethinylestradiol Jenapharm, Ethy 11, Eticyclin, Eticyclol, Eticylol, Etinestrol, Etinestryl, Etinoestryl, Etistradiol, Etivex, Follicoral, Ginestrene, Gynolett, Halodrin, Inestra, Jenapharm, Ethinylestradiol, Kolpolyn, Linoral, Lynoral, Marvelon, Menolyn, Mercilon, Microfollin, Neo-Estrone, Nogest-S, Novestrol, Oradiol, Orestralyn, Orestrayln, Oviol, Primogyn, Primogyn C, Primogyn M, Progynon C, Progynon M, Prosexol, Spanestrin, Varnoline, Ylestrol	adenomyosis/Unspecified phase amenorrhea/Phase 4 breast cancer/Approved
17-alpha-ethinylestradiol	ESR1, ESR2	activator	Amenoron, Amenorone, Cyclosa, Dicromil, Diognat-E, Diogyn E, Diogyn-E, Diprol, Dyloform, Ertonyl, Esteed, Estigyn, Estinyl, Eston-E, Estopherol, Estoral, Estorals, Ethidol, Ethinoral, Ethinyl-Oestradiol Effik, Ethinylestradiol Jenapharm, Ethy 11, Eticyclin, Eticyclol, Eticylol, Etinestrol, Etinestryl, Etinoestryl, Etistradiol, Etivex, Follicoral, Ginestrene, Gynolett, Halodrin, Inestra, Jenapharm, Ethinylestradiol, Kolpolyn, Linoral, Lynoral, Marvelon, Menolyn, Mercilon, Microfollin, Neo-Estrone, Nogest-S, Novestrol, Oradiol, Orestralyn, Orestrayln, Oviol, Primogyn, Primogyn C, Primogyn M, Progynon C, Progynon M, Prosexol, Spanestrin, Varnoline, Ylestrol	adenomyosis/Unspecified phase amenorrhea/Phase 4 breast cancer/Approved
4-hydroxytamoxifen	ESR1	antagonist		breast cancer/Unspecified phase ductal carcinoma in situ/Phase 2 estrogen receptor positive breast cancer/Phase 2

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Target Information - Overview of known drug targets in Canonical Pathway

Showing 3 of 60 row(s) of Target data.

Target (Gene Symbol)	Entrez Gene Name	Location	Type	Drug(s)	Species
Akt		Cytoplasm	group	afuresertib, AT13148, ipatasertib, MSC2363318A, ONC-201, SR-13668	Human, Mouse, Rat
AKT1	AKT serine/threonine kinase 1	Cytoplasm	kinase	archexin, ARQ 092, AZD5363, BAY1125976, enzastaurin, GSK2141795, ipatasertib, LY2780301, MK2206, MPT0E028, perifosine, triciribine, triciribine phosphate	Human, Mouse, Rat
AKT2	AKT serine/threonine kinase 2	Cytoplasm	kinase	BAY1125976, enzastaurin, triciribine, triciribine phosphate	Human, Mouse, Rat

Supporting References - References from which the Canonical Pathway was derived

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INGENUITY SYSTEMS