

The background features a dark blue field with intricate, wavy patterns of lighter blue and white lines. These lines form a grid-like structure that undulates across the frame, creating a sense of depth and movement. The overall aesthetic is modern and scientific.

# GLADSTONE INSTITUTES

# Introduction to Pathway Modeling

October 25, 2019

**GLADSTONE** INSTITUTES  
*SCIENCE OVERCOMING DISEASE*

# Goals and Motivations

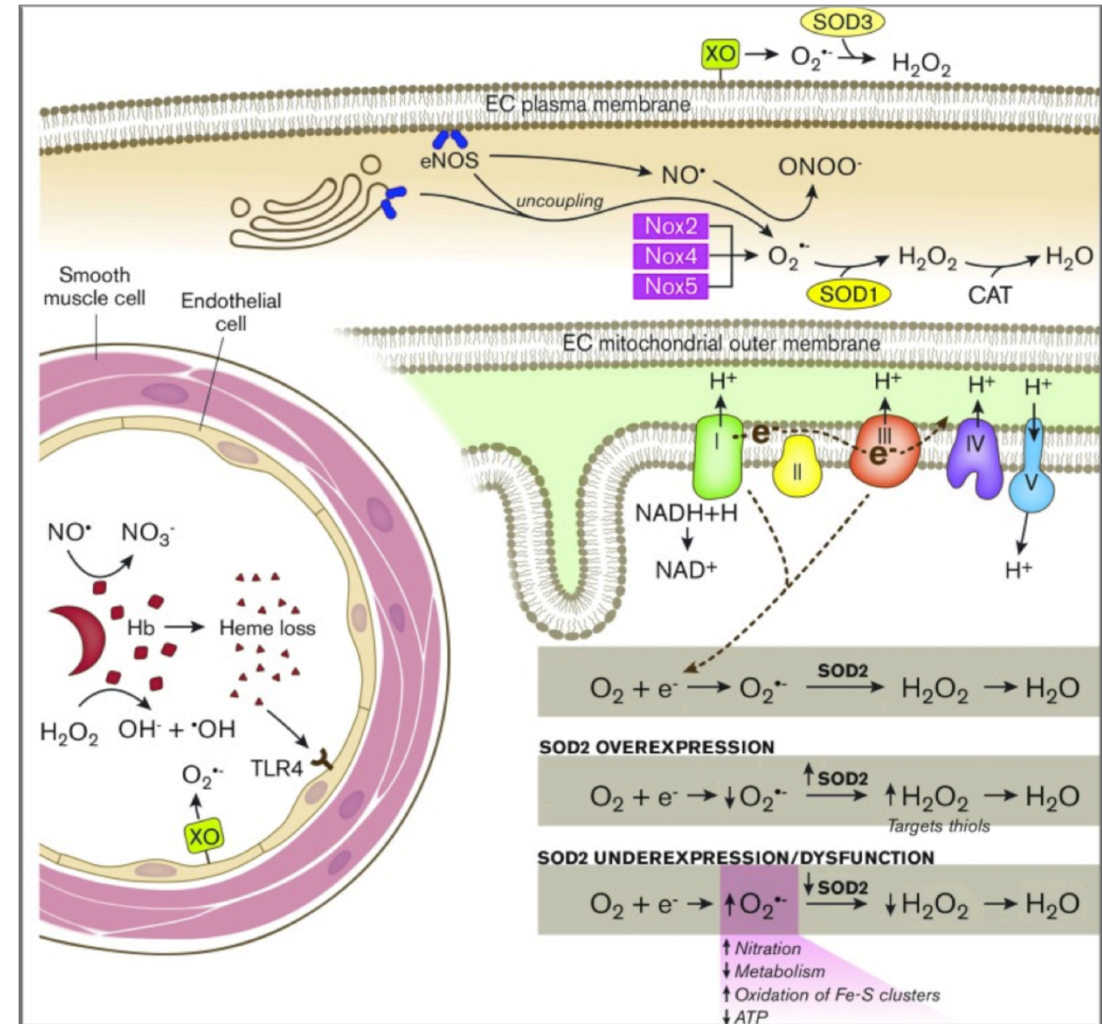
- Review how pathways are used in research
- Discover the advantages to computational pathway models
- Access existing pathway tools
- Learn how to use pathway drawing tools
- Create your own pathway models!

# Overview

- Introduction to Pathways in Research
- Guided Tour of Editing Tools
- Quality Control for WikiPathways
- Hands-on Session 1: Introduction
- Break
- Hands-on Session 2: Create Your Own Pathway

# Why Pathways?

- Intuitive representation of complex information
  - ➔ Over 1000 published each month
- Proteins / genes / metabolites
- Interactions / reactions
- Subcellular location



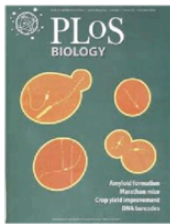
# Why Pathway Models?



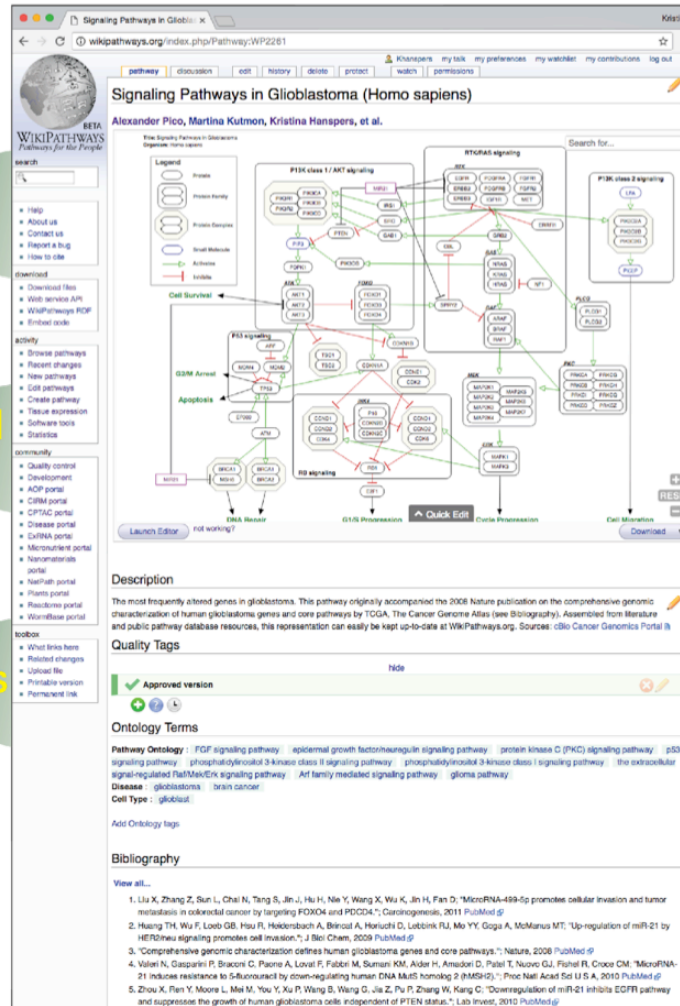
Literature



Experimental data



Static figures



Authorship

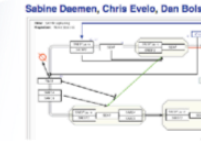
Figure images

Annotated models

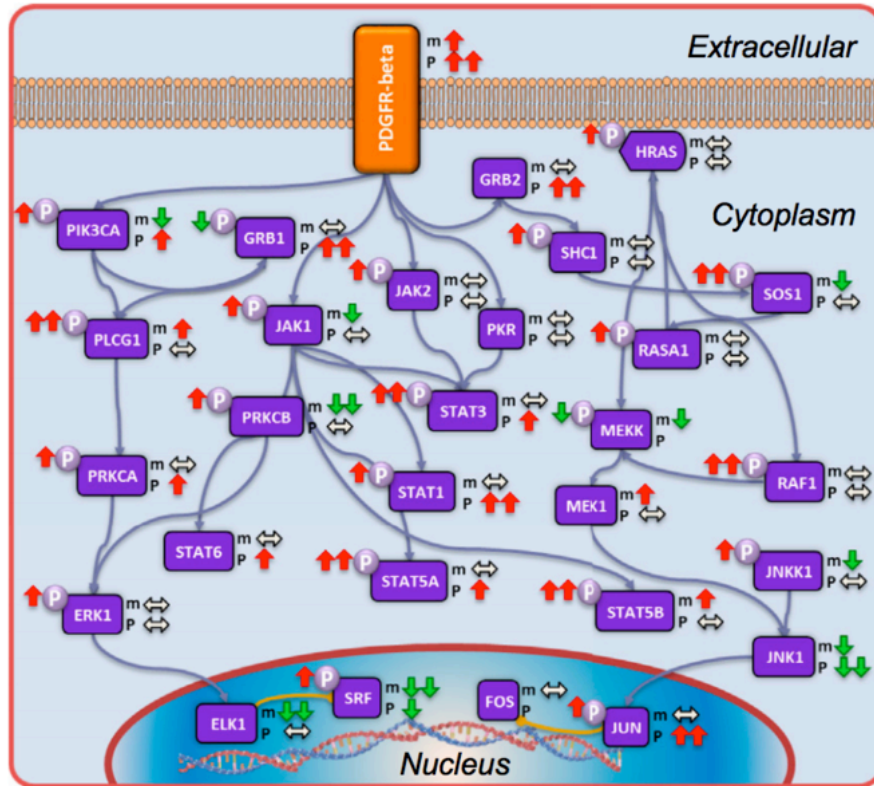
Visualization & analysis

Collaboration

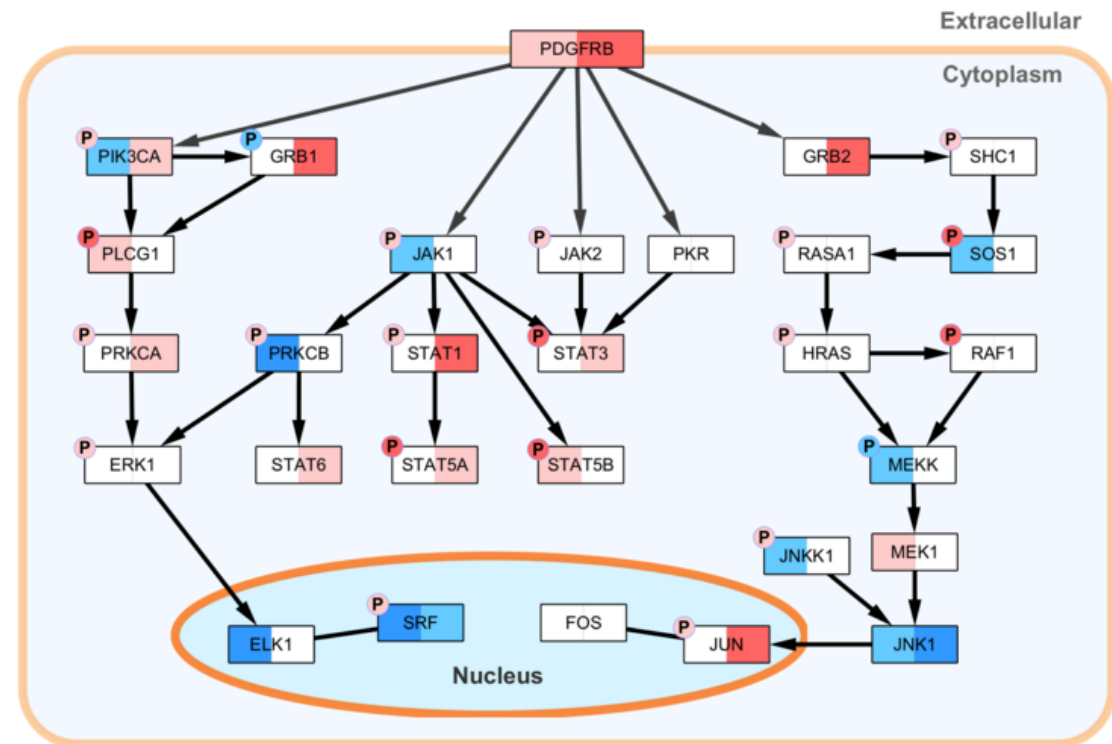
Distributed resource



# Data Visualization on Pathway Models

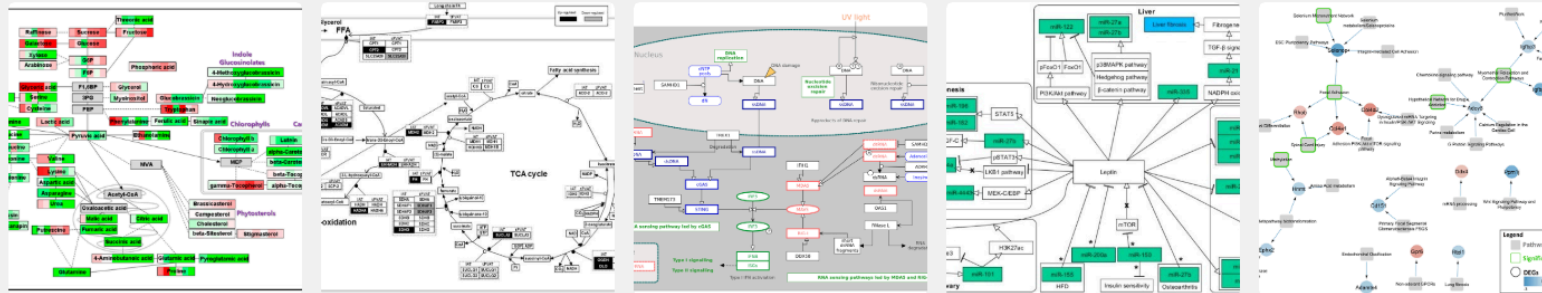


**Static image**  
*Zhang et al, Cell 2016*



**PDGFR-beta pathway with transcriptomic/  
phosphoproteomic data**  
*Zhang et al, Cell 2016*

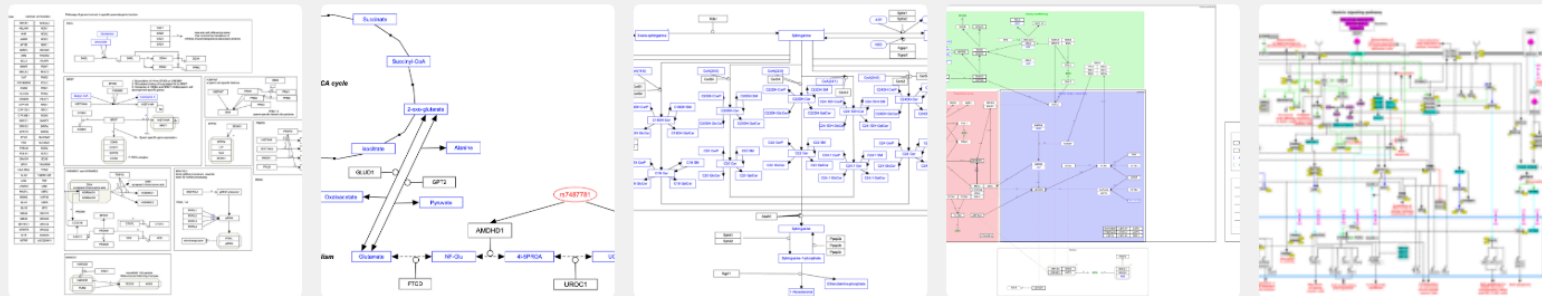
October 2019



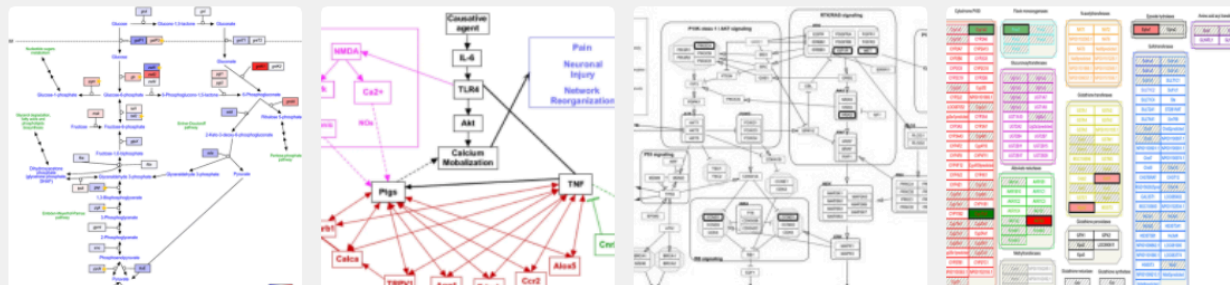
WikiPathways Publications

<http://wikipathways.tumblr.com/>

September 2019



August 2019





# Publishing Pathway Models



Bioinformaticia  
External tools  
Web services

WikiPathways

Network Info Nodes/Edges

WP1600 - Nicotine Metabolism - Homo sapiens

Nodes: 42 Edges: 31  
PUBLIC 🔍 Read Only [Copy URL](#)  
@context: view namespaces

Owner: WikiPathways Project  
Created: Sep 27, 2019 2:16:00 PM  
UUID: 01499db4-e16c-11e9-bb65-0ac135e8bacf  
Format: Unknown

Description: Nicotine results in many metabolites after metabolism in the liver. Nicotine is the main factor behind smoking addiction, therefore nicotine supplements can be used to stop smoking. Nicotine is metabolized by several enzymes in the liver such as the CYP2A6 enzyme. CYP2A6 is a xenobiotic (xenos = foreigner, bios = life) metabolizer. How well nicotine can be metabolized by the human body is not standard and depends on racial, gender, genetic and environmental factors. The cotinine metabolite seen above in the center of the nicotine metabolism pathway is a smoking biomarker and can be measured in various tissues such as blood, urine and sweat.

Rights Holder: WikiPathways  
Rights: Waiver-No Rights Reserved (CC0)  
Version: 20190927

Properties:  
author WikiPathways team  
cell hepatocyte  
labels WP1600, nicotine pathway, xenobiotic metabolic pathway, drug pathway  
networkType pathway  
organism Homo sapiens  
wikipathwaysID WP1600  
wikipathwaysIRI External Link

pathway discussion edit history delete protect unwatch permissions

TCA Cycle Nutrient Utilization and Invasiveness of Ovarian Cancer (Homo sapiens)

Kristina Hanspers, Alexander Pico, Denise Slenter, et al.

Legend

- Tyrosine phosphorylation pathway
- Serine phosphorylation pathway
- Metabol flux

Cancer stage → Low-invasive Ovarian Cancer → High-invasive Ovarian Cancer

Glucose → EGFR → JAK1 → STAT3 → Tyrosine phosphorylation pathway → Pyruvate → Lactate

D-Glutamine → ERK2/ERK1 → STAT3 → Serine phosphorylation pathway → TCA Cycle

Complex I NADH-Ubiquinone, Complex II Succinate-Ubiquinone

Launch Editor not working? Download

Description

Schematic showing the shift in nutrient utilization in TCA cycle with increasing degree of invasiveness. Low-invasive ovarian cancer (OVCA) cells are glucose dependent for their TCA cycle pool. With increasing invasiveness in cancer cells, dominant nutrient which feeds the TCA cycle shifts from glucose to Glin. In

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# Editing Tools: WikiPathways and PathVisio

[www.wikipathways.org](http://www.wikipathways.org)

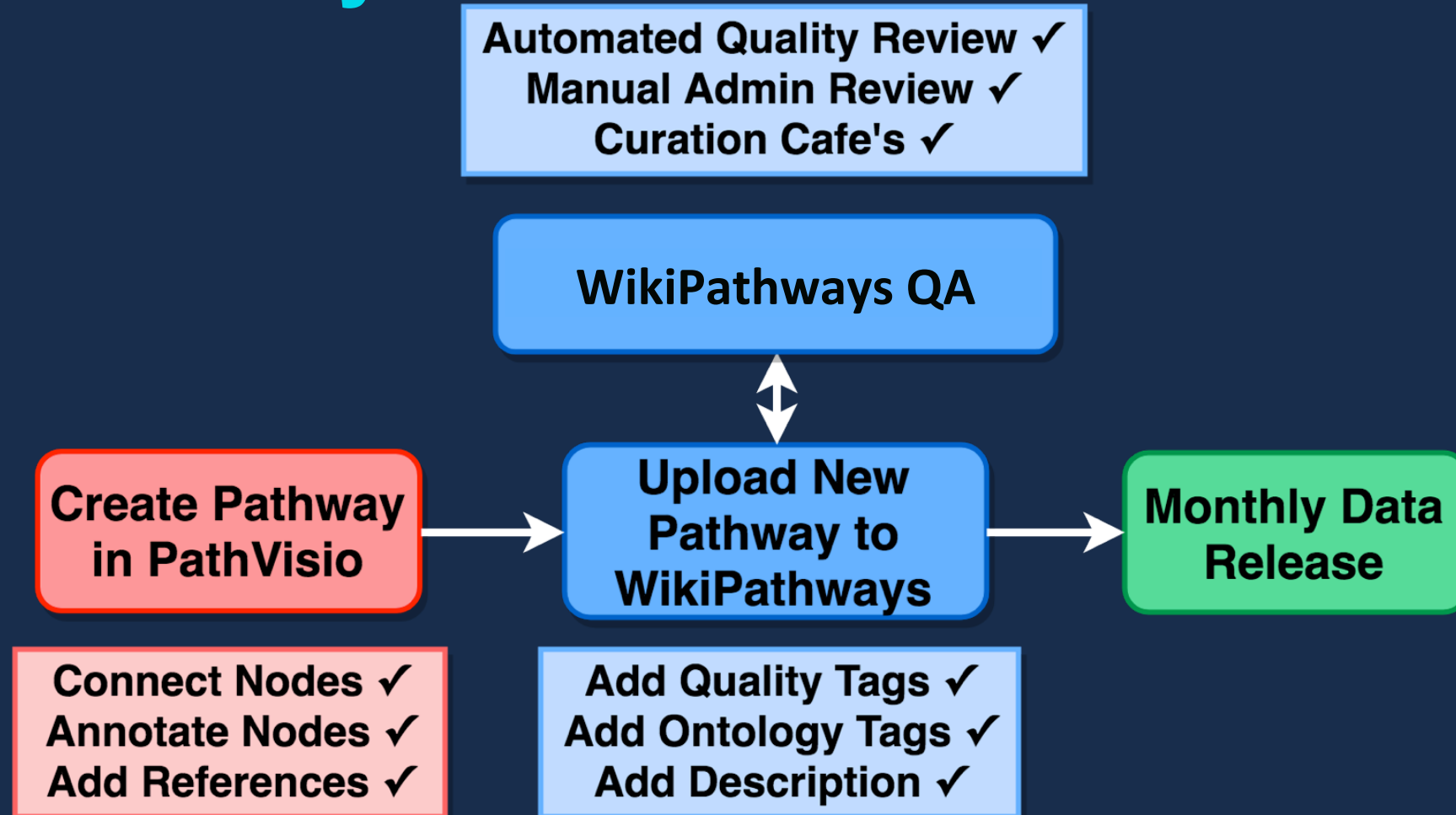
**miRNAs in the signaling pathway of the immune response in sepsis (Homo sapiens)**  
Kristina Hanspers, Egon Willighagen

**Description**  
Involvement of cellular miRNAs in the signaling pathway of the immune response in sepsis. Cellular immune miRNAs target important components of the NF- $\kappa$ B signaling pathway at different levels regulating the inflammatory response in the pathogenesis of sepsis. Lower part of the figure illustrates the pathophysiological events in sepsis that lead to tissue injury and subsequent multiple organs failure.

## PathVisio Desktop Software

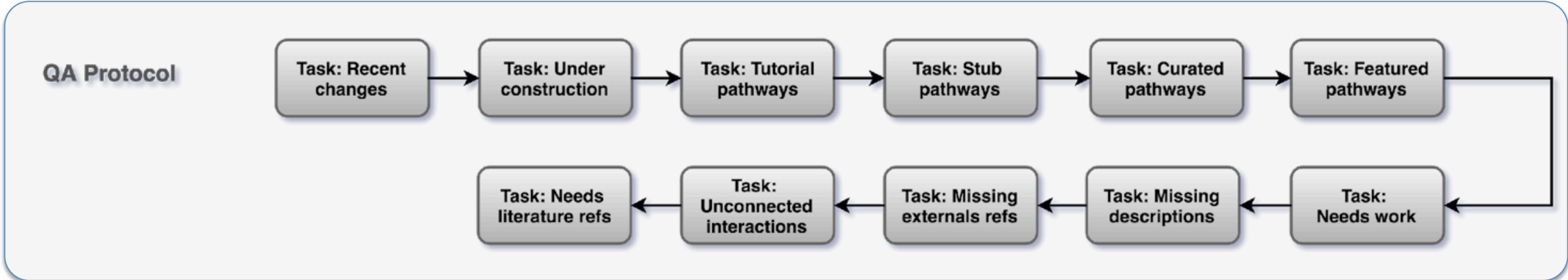
PathVisio Desktop Software interface showing the same pathway diagram as the WikiPathways website. The software interface includes a menu bar, a toolbar, and a sidebar with various tool options like 'Basic interactions', 'MM interactions', and 'Cellular compartments'. A blue arrow points from the WikiPathways website to the PathVisio software.

# Life Cycle of a Pathway Model at WikiPathways



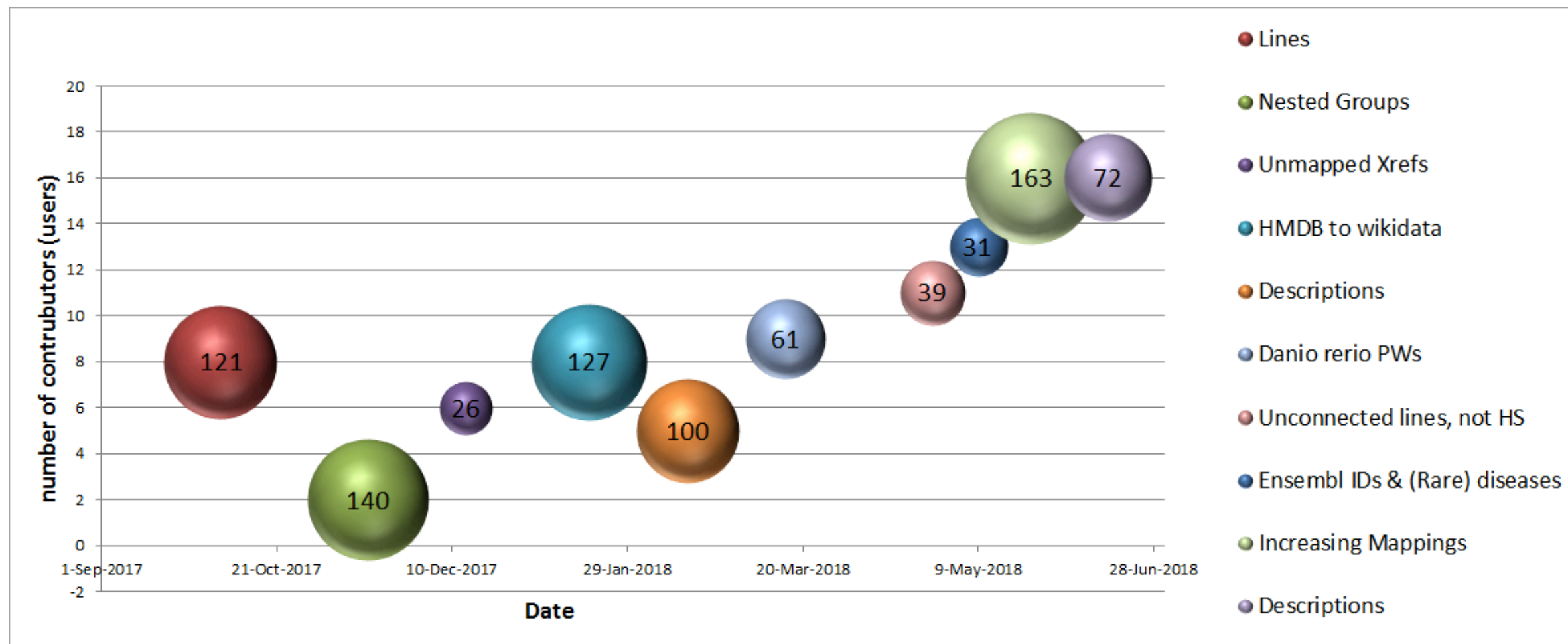
# Quality Control Protocol

## QA Team



<https://wikipathways.github.io/academy/qaprotocol.html>

# Focused QA Events



# WikiPathways Academy

[academy.wikipathways.org](http://academy.wikipathways.org)

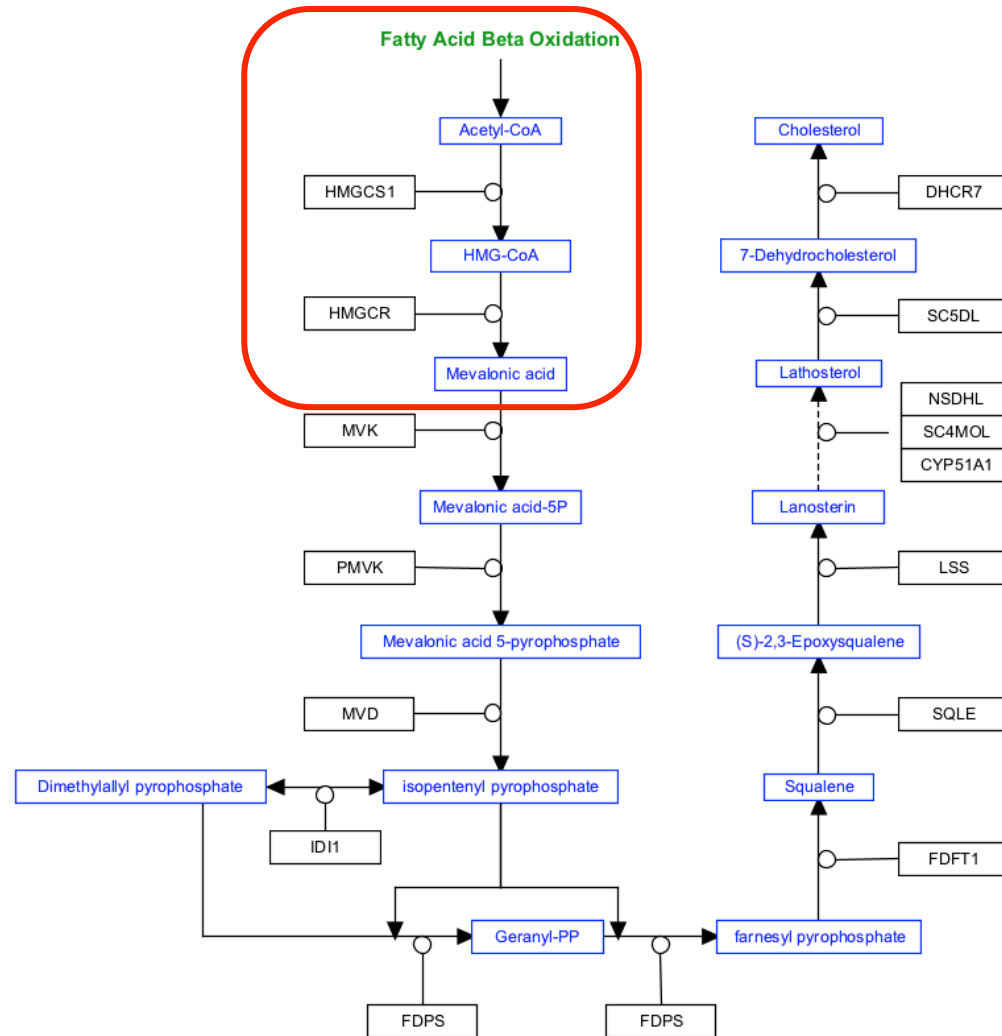


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# Drawing Challenge 1: Cholesterol Biosynthesis



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# Pathway Curation

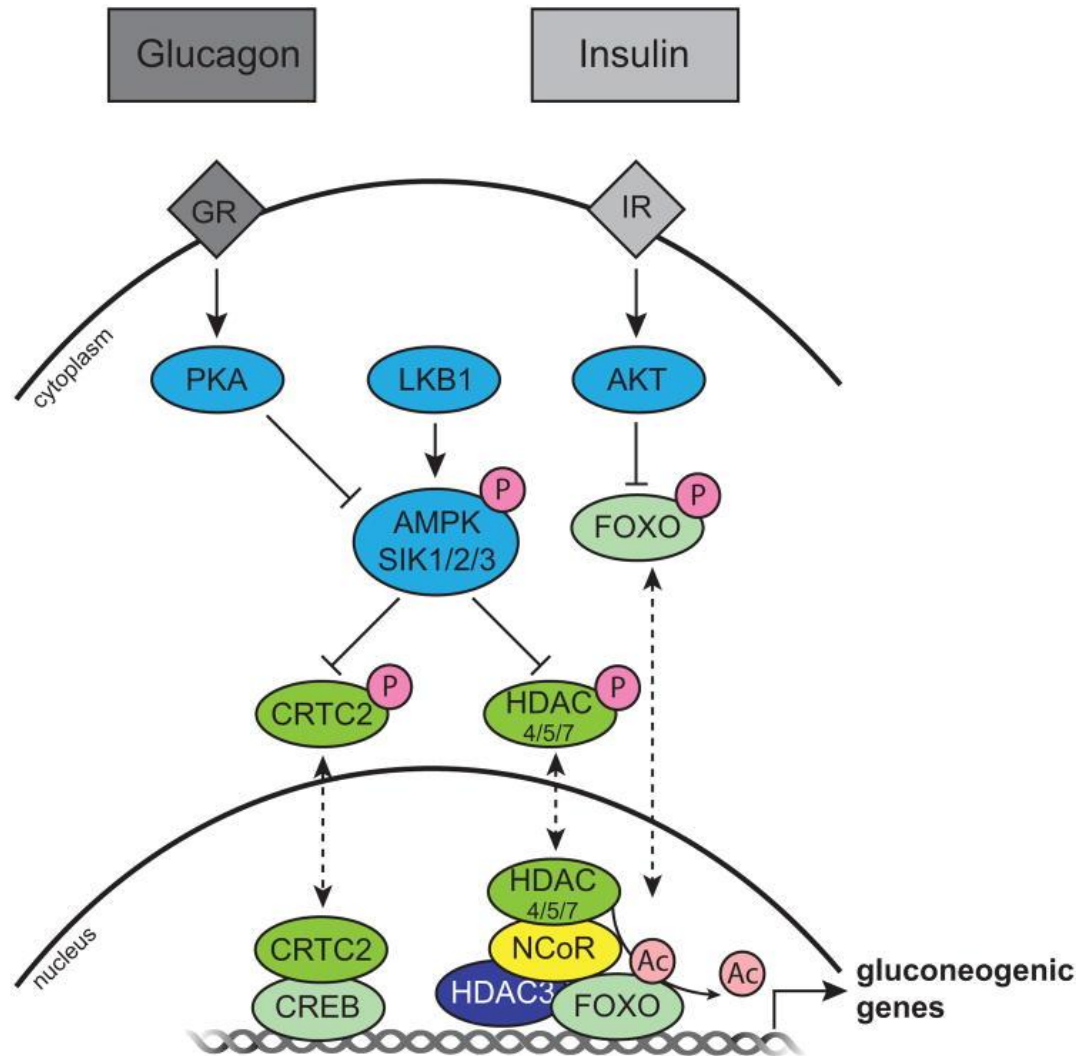
1. Identify a pathway topic
2. Find a model / use your own
3. Search WikiPathways
4. Make a curation plan!
  - Edit existing
  - Clone and mutate
  - New pathway

**What's the difference between you and a  
pathway curator?**

**NOTHING!**



# Example pathway 1: Kinase-mediated control of CRTC2 and HDAC4/5/7 subcellular localization and activity



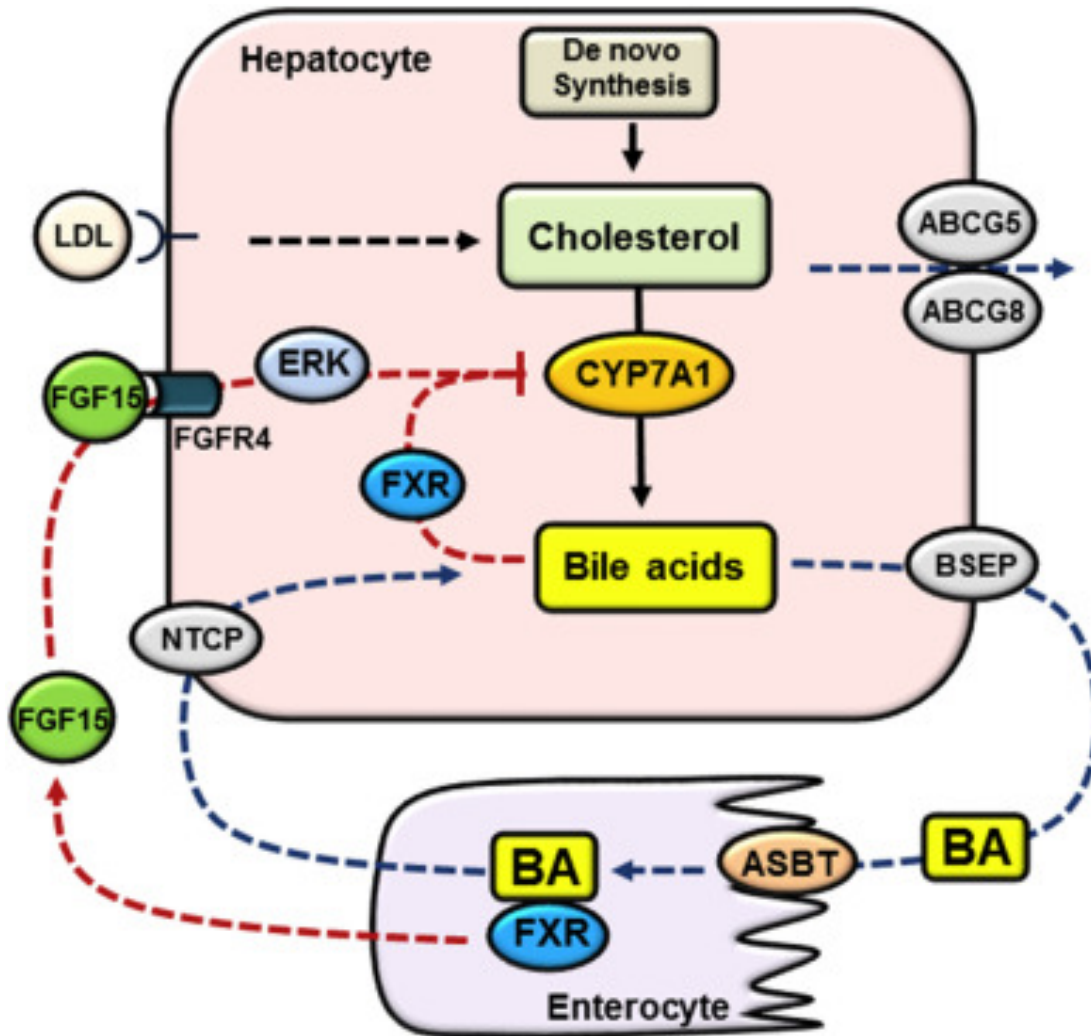
[Transcriptional coregulators: fine-tuning metabolism. Mouchiroud et al., Cell Metab, 2014, Figure 4.](#)

PMID: 24794975

Molecular model of kinase-mediated control of CRTC2 and HDAC4/5/7 subcellular localization and activity

The metabolic hormones glucagon and insulin signal through the glucagon receptor (GR) and insulin receptor (IR), respectively, to initiate signaling cascades downstream of changes in metabolic status. PKA and LKB1 phosphorylate (orange circles with a P) the AMPKRs (AMPK-Related Kinases), including AMPK and SIK1/2/3 which, when active, phosphorylate CRTC2 and HDAC4/5/7, resulting in their cytoplasmic sequestration. When unphosphorylated, CRTC2 and HDAC4/5/7 translocate to the nucleus (dashed lines) where they are free to promote the activation of gluconeogenic gene expression programs through CREB and the NCoR, HDAC3, FOXO complex, respectively. CRTC2 coactivates CREB, and nuclear FOXO is activated upon HDAC4/5/7-mediated deacetylation (light pink circles). In parallel, AKT phosphorylation regulates the activity of FOXO.

## Example Pathway 2: Bile acid synthesis and enterohepatic circulation

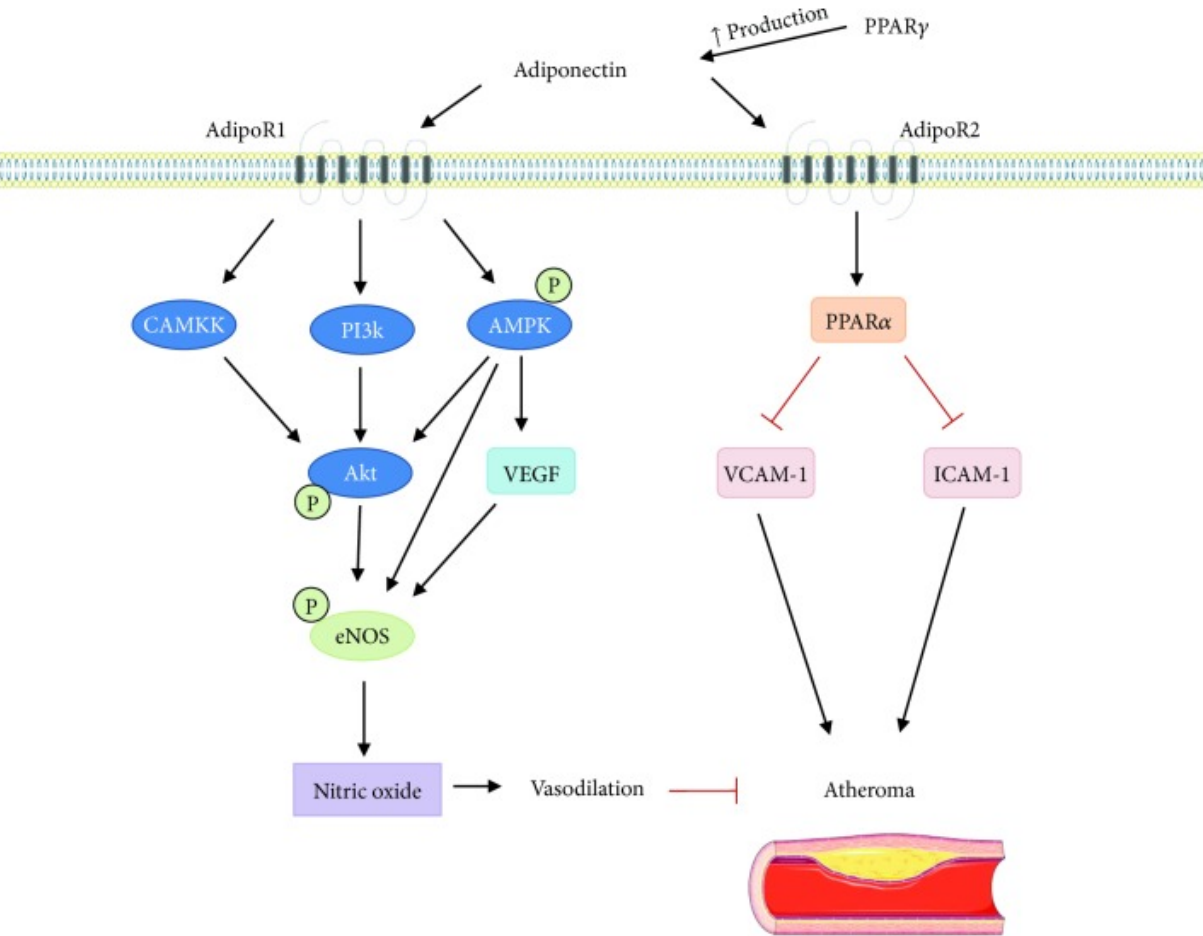


[Cholesterol and bile acid-mediated regulation of autophagy in fatty liver diseases and atherosclerosis. Wang et al, Biochim Biophys Acta Mol Cell Biol Lipids 2018, Figure 1](#)

PMID: 29653253

**Bile acid synthesis and enterohepatic circulation.** Hepatocytes acquire cholesterol via de novo synthesis and receptor-mediated endocytosis of cholesterol-rich lipoproteins. Hepatocytes eliminate cholesterol via bile acid synthesis and biliary secretion of cholesterol via ABCG5/ABCG8. Bile acids are synthesized from cholesterol in hepatocytes. CYP7A1 catalyzes the first and rate-limiting step in cholesterol conversion into bile acids. Bile acids are secreted into the bile via BSEP and subsequently released into the small intestine. The majority of bile acids is re-absorbed into the enterocytes via ASBT and transported back to the liver via portal circulation. Basolateral NTCP transports conjugated bile acids into the hepatocytes. Bile acids in the hepatocytes activate FXR to inhibit CYP7A1. Bile acids in the small intestine activate FXR to induce FGF15, which binds and activates FGFR4 to inhibit CYP7A1 partially via ERK signaling.

# Example Pathway 3: Proposed signaling mechanisms of adiponectin in prevention of ischemic stroke



[Role of Adiponectin in Central Nervous System Disorders, Boemer et al Neural Plast. 2018, Figure 2.](#)

PMID: 30150999

**Proposed signaling mechanisms of adiponectin in prevention of ischemic stroke.** Signaling through AdipoR1 and AdipoR2 can reduce formation of atheroma. AdipoR1 activates the AMP-activated protein kinase (AMPK) pathway resulting in phosphorylation of protein kinase B (Akt) and activation of vascular endothelial growth factor (VEGF). Activation of Akt through calcium calmodulin kinase kinase (CAMKK), phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K), and AMPK contributes to activation of endothelial nitric oxide synthase (eNOS). Additionally, AMPK and VEGF also increase eNOS activity leading to nitric oxide (NO) production. Increase in production of NO leads to vasodilation, which is beneficial in prevention of atheroma and ischemia. Adiponectin signaling reduces vascular cell adhesion molecule 1 (VCAM-1) and intracellular adhesion molecule 1 (ICAM-1), and these adhesion molecules increase atheroma size. Peroxisome proliferator-activated receptor alpha (PPARα) also reduces VCAM-1 and ICAM-1, and PPARα is activated by AdipoR2 signaling. PPARγ increases production of adiponectin and also leads to reduction of VCAM-1 and ICAM-1. This figure was produced using Servier Medical Art (<http://www.servier.com/>).



# Questions?

[kristina.hanspers@gladstone.ucsf.edu](mailto:kristina.hanspers@gladstone.ucsf.edu)

The background of the image is a microscopic view of cells, likely from a tissue sample. The cells are stained in shades of blue and cyan, with some appearing as bright, glowing spots against a darker blue background. The overall texture is organic and complex, resembling a network of interconnected cells.

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