**β-arrestins**

Arrestins consist of four classes, including β-arrestin 1 and β-arrestin 2. Both β-arrestin 1 and β-arrestin 2 are key negative regulators, multifunctional signal transducer, and scaffolds of G protein-coupled receptors (GPCRs) signaling. However, role of β-arrestin in the development of human diseases remain to be defined.

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Critical involvement of beta-arr 1 in experimental autoimmune encephalomyelitis (for multiple sclerosis)

Beta-Arr2 Deficiency Promotes Lung Tumor Growth, Lung Metastasis, and Mortality

Inhibition of lung tumor growth in mice treated with CXCR2-neutralizing Abs or NF-kappaB-inhibitor

Rapid hepatocellular tumor growth in β-Arr1 transgenic mice


Blockage of rapid hepatocellular tumor growth by MMP9 inhibitors in Beta-Arr1 transgenic mice

Effect of β-arrestin 1 on colon cancer migration and invasion in vitro and metastasis in vivo

Model of β-arrestin Mediated Migration and Metastasis

β-Arrestin-2 regulates the development of allergic asthma

β-Arrestin-2 regulates allergic airway disease
Am J Respir Cell Mol Biol. 2009 Oct 5. [Epub ahead of print]
Beta-arr1 expression was increased significantly from primary biliary cirrhosis (PBC) patients. Beta-arr1 contributes to the pathogenesis of PBC patients.


Role of beta-arrestin 2 in hepatocyte apoptosis

- The mechanisms for hepatocyte apoptosis following bile duct ligation (BDL) are incompletely understood.
- beta-arrestin 2, initially recognized as scaffold protein in termination of GPCR signaling through receptor endocytosis, is closely with cell survival signaling by an unknown mechanism.
- The role of beta-arrestin 2 in hepatocyte apoptosis in cholestatic liver diseases is unknown.
- Akt, GSK3beta and p38 have been shown to mediate beta-arrestin 2 signaling of survival.

Materials and Methods

- Animal Model: 6-8-week-old Wild type (WT) and beta-arrestin 2 knockout (KO) male mice
- Groups: 1. WT Sham; 2. WT+BDL; 3. beta-arrestin 2 KO Sham and 4. beta-arrestin 2 KO+BDL
- Time: BDL 3d, 7d and 14d
- Hepatocyte Apoptosis: TUNEL Assay, Immunohistochemistry for caspase 3
- Liver Injury: H&E and Sirius Red Staining of Liver Sections

Akt regulates cellular activation, inflammatory response, and apoptosis. Activated Akt phosphorylates several downstream targets of the PI3K signaling pathway such as GSK3beta.

GSK3beta plays a pivotal role in regulating many cellular functions, including cell survival and apoptosis.

Mitogen-activated protein kinases (MAPKs) mediate the signaling of various biological events that include development, proliferation, differentiation and apoptosis. the p38 (MAPK) pathway are activated by cellular stress, for example reactive oxygen species (ROS), and regulate cellular processes such as apoptosis.
Deficiency of β-arrestin 2 Enhances Survival After BDL

Survival of WT and β-arrestin 2 KO mice were observed from 5 to 30 days after BDL. Survival of WT mice was reduced compared to β-arrestin 2 KO mice.

B. Gallbladder morphology in WT and β-arrestin 2 KO mice.

Hepatocyte Apoptosis is Reduced in β-arrestin 2 KO Mice Following BDL

Hepatocyte apoptosis was determined by both Tunel assay and immunohistochemistry for cleaved-caspase3 in livers from WT and β-arrestin 2 KO mice. Tunel assay showed the increased apoptotic cells due to BDL were reduced in β-arrestin 2 KO mice. (*p<0.01, β-arrestin 2 KO vs WT). The increased number of cleaved-caspase3 positive hepatocytes due to BDL were reduced in β-arrestin 2 KO mice (*p<0.01, β-arrestin 2 KO vs WT).
The Reduced Liver Injury in β-arrestin 2 KO Mice is Associated With Increased Levels of p-Akt and p-GSK3β, but not p-p38.

The degree phosphorylation of β-arrestin 2 associated survival signals was determined by Western blot. A. β-arrestin 2 is upregulated by BDL and absent in KO mice. B. Phosphorylated p-38 (p-p38) is upregulated by BDL in WT mice but not β-arrestin 2 KO mice following BDL. C. p-Akt and p-GSK3β are upregulated following BDL significantly higher in β-arrestin 2 KO mice vs WT mice following BDL. (*p<0.01 by indicated group). Since Akt and GSK3β are associated with cell survival, higher values in KO mice may indicate their roles in reducing injury in β-arrestin 2 KO mice.

Administration of GSK3β Inhibitor Attenuates Hepatocyte Apoptosis Due to BDL in WT but not in β-arrestin 2 KO Mice.
To determine whether the increased levels of p-GSK3β (the inactive form) in β-arrestin 2 KO mice is required for inhibiting apoptosis, we tested the effect of SB216763, a GSK3β inhibitor on degree of liver injury. Both the increased number of TUNEL positive and cleaved-caspase3 positive cells were reduced by the SB216763 in WT but not β-arrestin 2 KO mice. Data are consistent with active GSK3β (the dephosphorylated form) potentiating apoptosis following BDL.

The GSK3β inhibitor, SB216763 increases GSK3β phosphorylation (inactive GSK3β) in both WT and β-arrestin 2 KO mice.

**Conclusions**

1. Deficiency of β-arrestin 2 protects hepatocytes from the apoptosis following BDL.

2. Loss of β-arrestin 2 is associated with phosphorylation (inactivation) of GSK3β.

3. Inhibition of GSK3β reduces liver injury after BDL.

4. β-arrestin 2/GSK3 are new potential targets for the treatment of cholestatic diseases.
Proposed Pathway for β-arrestin 2-dependent Apoptosis

Supporting evidence:
1. β-arrestin 2 is upregulated in BDL mice.
2. β-arrestin 2 KO mice have reduced injury after BDL associated with the downregulation of GSK3β activity.
3. GSK3 inhibitor prevents liver injury after BDL in WT but not β-arrestin 2 KO mice.

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