Cell Research (2009) 19:275-276.

www.nature.com/cr

RESEARCH HIGHLIGHT

# Insulin resistance: β-arrestin development

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*Cell Research* (2009) **19**:275-276. doi: 10.1038/cr.2009.22; published online 2 March 2009

Insulin resistance is simply the inability of insulin to elicit a physiologic response. While insulin resistance is most commonly associated with the pathogenesis of metabolic disorders such as type II diabetes and obesity, it is also a predisposing factor to a number of other diseases such as cancer and cardiovascular disease [1]. There are just as many theories as to the cause of insulin resistance as there are insulin signaling molecules and it is very unclear as to which are the actual molecular mechanisms of insulin resistance in diseased states. In a recent paper Luan and colleagues present a novel finding that down-regulation of the β-arrestin 2 signaling molecule in insulin resistant/diabetic mice and humans may be an underlying cause [2].

Hyperglycemia and glucose intolerance are perhaps the most common pathophysiologies associated with diabetes and insulin resistance and can largely be due to initial dysregulation of liver and skeletal muscle metabolism. Skeletal muscle accounts for the vast majority of insulin-stimulated glucose disposal in the body and the liver acts as the main buffer in systemic glucose homeostasis through insulin-mediated suppression of gluconeogenesis and stimulation of glycogenesis. In fact, mouse models with tissue-specific defects in liver and/or skeletal muscle insulin signaling are sufficient to recapitulate the diabetic phenotype (reviewed in [1]). It is obvious that studying insulin signaling in these tissues will lead to a better understanding of metabolic disorders.

In line with this thinking Luan *et al*. [2] found that β-arrestin 2 and to a lesser extent β-arrestin 1 are down-regulated in the liver and skeletal muscle of insulin resistant and type II diabetic mouse models (*db/db* and high fat fed diet induced obesity). Additionally, they show that both β-arrestin 1 and 2 are down-regulated in the livers of type II diabetic humans. While β-arrestin 1 and 2 are rather well described signaling adapter molecules, they are not generally associated with insulin signaling. Most of the previous work on β-arrestins has described them as components of G-protein coupled receptor (GPCR) signaling. Following agonist-induced stimulation of GPCRs, β-arrestins bind to the cytoplasmic tails of GPCRs and prevent reactivation, a process known as desensitization. However, Luan and colleagues [2] present new data demonstrating that β-arrestin 2 plays a crucial role in the downstream signaling of the receptor tyrosine kinase (RTK), insulin receptor (InsR).

Based on their findings in diabetic mice and humans, Luan *et al*. [2] hypothesized that β-arrestin 2 may have a role in insulin signaling and resistance. The authors observe that β-arrestin 2 knock-out (β-arr2-KO) mice display post-prandial hyperglycemia and glucose and insulin intolerance, all of which are hallmarks of diabetes and insulin resistance. Additionally, they found that the diabetic phenotype of *db/db* and β-arr2-KO mice can be alleviated by adenoviral expression of β-arrestin 2 in the liver, suggesting that insulin sensitivity can be restored by re-introduction of β-arrestin 2. Consistent with the results in β-arr2-KO mice, whole body β-arrestin 2 transgenic (β-arr2-Tg) mice display the opposite phenotype. β-arr2-Tg mice are glucose and insulin sensitive and display post-prandial hypoglycemia despite no changes in food intake. These results suggest that β-arrestin 2 plays a significant role in insulin signaling.

Indeed, when the authors analyzed insulin signaling in the livers of β-arr2-KO they found strong defects in insulin-stimulated phosphorylation of Akt, GSK3, and Foxo1, which are classic targets that mediate many of the metabolic affects of insulin, consistent with previous reports [3]. Conversely, in β-arr2-Tg mice they found enhanced insulin-stimulated phosphorylation of these targets.

To answer how β-arrestin 2 functions in the insulin signaling pathway, they apply a similar model of β-arrestin 2's function in the MAPK signal transduction. β-arrestin 2 is well described as a scaffold molecule required for GPCR-mediated activation of several kinases such as Src, ERK1/2, MEK and many others, where it can bind to several kinases at once, bringing them into close

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proximity and facilitating signal transduction (reviewed in [4, 5]). Consistent with previous reports the authors found that β-arrestin 2 interacts with Akt [6], Src [7], and InsR. Taking this a step further, they show that β-arrestin 2 forms a complex with Akt, Src, and InsR that assembles in response to insulin signaling and is required for full activation of Akt. Putting this together, the authors propose a model in which β-arrestin 2 serves as a scaffold molecule bringing several components of insulin signaling together at near the site of signal initiation. However, more work needs to be done to further characterize these interactions, and it would be interesting to study the effect of β-arrestin 2 on Src and Akt localization. For instance, the well characterized PH domain of Akt as well as the phospho-tyrosine binding SH2 domain of Src, have been shown to be essential for membrane localization and activation.

While this is a novel function of β-arrestin 2, there are hints that β-arrestin 1 may function in a similar manner. Studies from several laboratories have shown that β-arrestin 1 binds to InsR and IGF-1 receptor very rapidly after ligand activation, and that β-arrestin 1 may play a role in desensitization and turnover of the InsR and IGF-1R [5]. Furthermore, it has been shown that prolonged insulin stimulation of cells causes enhanced β-arrestin 1 degradation [8]. In the future it will be important to analyze the temporal involvement of β-arrestin 2 in insulin signaling. In GPCR signaling β-arrestins are involved in the signal transduction, signal termination, and receptor internalization steps following stimulation; and insulin receptor undergoes analogous steps following stimulation [4]. Another interesting avenue to explore would be the dynamics of Akt activation. Currently, the mechanism and dynamics of Akt phosphorylation/dephosphorylation in the liver are unclear; an interesting note is that β-arrestin 2 has been shown to interact with Akt and PP2A phosphatase and is involved in Akt dephosphorylation in dopaminergic neurons [6]. It may be worth investigating if β-arrestin 2 may mediate a similar interaction at later time points following insulin stimulation in the liver. Down the road, a crucial question is to determine whether down-regulation of β-arrestin 2 occurs before or after signs of glucose intolerance and insulin resistance. This might answer a potential causative role of β-arrestin 2 in diabetes.

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