

## Insulin receptor-related receptor in the pancreas and in a $\beta$ -cell line

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Insulin receptor-related receptor (IRR) belongs to the family of the insulin receptor (IR) along with the IR itself and the insulin-like growth factor receptor. Whereas the ligands of the latter receptors are known, identification of an IRR ligand has eluded investigations so that IRR has been considered an orphan receptor. A recent breakthrough in the understanding of IRR functional role came from the finding that IRR can be activated by mildly alkali media in absence of any protein agonist [1]. IRR shows highly specific tissue distribution, with highest concentration in kidney intercalated cells. However, significant amounts of the receptor are also found in the stomach and in  $\alpha$ - and  $\beta$ -cells of the islets of Langerhans. Recent reports indicate that the pancreatic duct system is frequently associated with islet cells. Here, we show that those islet cells that are in contact with the excretory ducts are also IRR-expressing cells. Thus, when the exocrine pancreas is in an active state of secretion duct-associated islet cell behavior is potentially influenced by an IRR-mediated alkaline-induced signalling pathway. To explore this issue, we analyzed the effects of alkaline media on the pancreatic  $\beta$ -cell line MIN6. Activation of endogenous IRR was detected and could be inhibited with linsitinib, a synthetic inhibitor of the IR family of receptors. IRR autophosphorylation correlated with pH-dependent linsitinib-sensitive activation of IR substrate 1 (IRS-1). In contrast to insulin stimulation, no protein kinase B (Akt/PKB) phosphorylation was detected as a result of the alkali treatment. The alkaline medium but not insulin also triggered actin cytoskeleton remodeling in MIN6 cells that was blocked by pre-incubation with linsitinib. We propose that the activation of IRR by alkali is a component of a local loop of signaling between the exocrine and endocrine parts of the pancreas.

### References

- [1] Deyev et al. (2011) Insulin receptor-related receptor as an extracellular alkali sensor. *Cell Metabolism* 13: 679-689

### Keywords

Insulin receptor-related receptor, MIN-6 cells, pancreas, insulin-secreting cells, insulin receptor substrate 1, immunofluorescence, western blotting