

CO-OPERATION BETWEEN EPIDERMAL GROWTH FACTOR RECEPTOR AND GLUCAGON-LIKE PEPTIDE 1 RECEPTOR IN PANCREATIC β -CELL SURVIVAL DURING OXIDATIVE STRESS

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The endocytic pathway is a pivotal regulator of *epidermal growth factor receptor (EGFR)* signalling. Upon interaction with ligands such as epidermal growth factor, *EGFR* dimerises, leading to receptor activation as well as internalisation by endocytosis and signal downregulation via lysosomal degradation of the receptor.¹

We have previously investigated the existence of an alternative route of *EGFR* trafficking following exposure to oxidative stress, in which *EGFR* is internalised in a clathrin adaptor AP2 and p38 mitogen-activated protein kinase-dependent manner in the absence of ligands, and segregates away from ligand-bound *EGFR* by the action of the endosomal actin regulator WASH into a distinct population of signalling endosomes where it delays apoptotic onset.^{2,3}

EGFR signalling defects have previously been implicated in the development of diabetes; transgenic mice expressing a mutated *EGFR* under the pancreatic duodenal homeobox-1 promoter,⁴ as well as adult mice which have had specific deletion of *EGFR* in their β -cells,⁵ display impaired postnatal β -cell proliferation, while *in vivo* expression of constitutively active *EGFR* improves glycaemia and markedly inhibits streptozotocin-triggered β -cell apoptosis.⁶ In addition, *EGFR* activity can be modulated via transactivation by the incretin receptor *glucagon-like peptide 1 receptor (GLP1R)* in pancreatic β -cells.⁷

The aims of this project are to analyse: 1) whether *EGFR* is implicated in protection against β -cell death by oxidative stress, triggered by exposure to pro-inflammatory cytokines and/or glucolipotoxicity; 2) whether a similar ligand-independent, oxidative stress-triggered *EGFR* trafficking response to the one described above is operational in pancreatic β -cells and if it contributes to the aforementioned protection; 3) whether similar agonist-independent responses apply to *GLP1R*; and 4) any possible receptor cross-talk between *EGFR* and *GLP1R* under stress conditions in pancreatic β -cells.

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