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Elucidating the biology of G-protein coupled receptor 35

Stöbern

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Öffnen

Thesis (PDF, 111Mb)

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Zusammenfassung

G-protein coupled receptor 35 (GPR35) is an orphan G-protein coupled receptor which has attracted attention as a coding variant is linked to primary sclerosing cholangitis (PSC) and ulcerative colitis (UC). GPR35 is also upregulated in numerous cancers. Multiple studies of GPR35 have so far fallen short of revealing its core biology. In this project we set out to gain further understanding of the biology of GPR35. Starting with unbiased protein interaction studies, we showed that GPR35 forms a heterodimer with the sodium-potassium ATPase (Na⁺/K⁺ATPase), a cornerstone of ion homeostasis. Using macrophages derived from Gpr35^{+/+} and Gpr35^{-/-} mice, we demonstrated that GPR35 significantly increases the ion transport function of Na⁺/K⁺ATPase in a ligand independent manner, an effect which appears to be mediated via a direct protein-protein interaction. This was found to have expected knock on effects on ion homeostasis as well as affecting whole cell metabolism including glucose uptake, glycolysis and mitochondrial respiration. Using macrophages derived from CRISPR edited human induced pluripotent stem cells, we found the T108M PSC/UC risk associated coding polymorphism to be hypermorphic in this regard. Furthermore, lack of GPR35 reduced intestinal epithelial cell proliferation at baseline and reduced tumour formation in intestinal cancer models. siRNA knockdown of GPR35 in Hep-G2 cells led to reduced cellular proliferation which was found to be related to osmotic stress, as shown by activation of the p38 MAPK pathway and rescue of the proliferative defect in a low salt environment. Finally, we performed large scale purification of the GPR35:Na⁺/K⁺ATPase heterodimer in an effort to elucidate its structure using cryogenic electron microscopy.

Keywords

G-protein coupled receptor 35, GPR35, Ulcerative colitis, Primary sclerosing cholangitis

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