ABSTRACT

Fam84b is a largely unstudied protein, where its function in eukaryotic cells is unclear. This thesis work presents a FAM84B knockout mouse model and characterises the resulting retinal phenotype in detail. FAM84B KO mice were morphologically assessed by optical coherence tomography and histological processing, revealing dynamic changes stemming from the photoreceptor and pigmented epithelial layers. This potent phenotype progresses with age, spreading inwards towards the inner retinal layers, as well as laterally to adjacent retinal regions. Comparative localisation of standard retinal cell markers demonstrates that FAM84B KO retinal layering becomes increasingly disorganised, together with deformation of the retinal macrostructure. Due to this, KO mice experience reducing responses to light, as demonstrated by electroretinography, where overall retinal efficiency falls. Fam84b shows homology to the HRASLS enzyme family, which are capable of attenuating Ras-associated signalling. To investigate whether Fam84b possesses a similar function, the level of phosphorylated and activated downstream Ras effectors were compared between wild type and FAM84B KO mouse retinal lysates. A reduction of pERK1 (pY204) in KO lysates suggests that Fam84b holds some function related to this pathway downstream of Ras. Preliminary co-immunoprecipitation experiments revealed a specific interaction between Fam84b and GRIPAP1, a neuronal scaffold for the JNK pathway, which may provide a crucial link between the elusive Fam84b and the destructive retinal degeneration present in its absence.

Key words

Fam84b, retina, degeneration, Ras, MAPK, Ras signalling, knockout, mouse