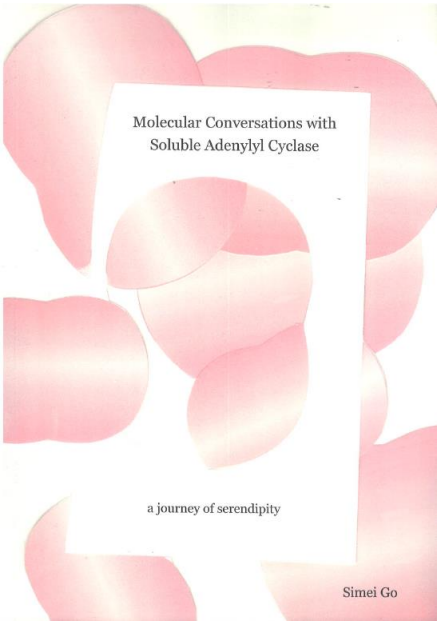

Samenvatting proefschrift
S. Go

'Molecular conversations with soluble adenylyl cyclase: a journey of serendipity'

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This thesis focuses on soluble adenylyl cyclase (sAC). Adenylyl cyclases (ACs) are enzymes that produce intracellular signaling molecule called cyclic AMP (cAMP). As a signaling molecule, cAMP activates other intracellular proteins; thereby forming a signaling cascade that leads to adaptations in cellular behavior. The most well-known signal that leads to AC activation, specifically those localized at the plasma membrane, are via hormone signaling. In this regard, sAC in unique because it localizes within the cell and is regulated by intracellular signals, including bicarbonate, calcium and ATP levels.

In this thesis we first investigated how sAC is regulated in cholangiocytes, the epithelial cells lining the bile duct. We found that the sAC protein carries sugar chains, which is unexpected since this type of modification is selective for groups of proteins not previously associated with sAC. We further demonstrate that sAC is secreted into extracellular vesicles, implying that sAC signaling could also be involved in intercellular communication. Within cholangiocytes, we demonstrate that sAC plays a critical role in relaying cell death signals during exposure of cholangiocytes to toxic bile salts. Exposure of cholangiocytes to bile salts leads to cell death, which can be mitigated when sAC is inhibited. This implies that sAC could play a role in the pathogenesis of primary biliary cholangitis. Finally, we also demonstrate that inhibition of sAC alters the S17 phosphorylation of SEC61β. Mutations in SEC61β lead to polycystic liver disease due to dysregulated maturation of polycystin-1. We demonstrate that absence of sAC signaling also interferes with polcystyin-1 maturation, and impairs the formation of a cellular antennae called the primary cilium. Both dysregulated polycystin-1 maturation and formation of the cilia have been implicated in polycystic liver disease.
The observations in this thesis imply an important role for sAC in cholangiocyte homeostasis that could be further investigated and exploited for therapeutic purposes.

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