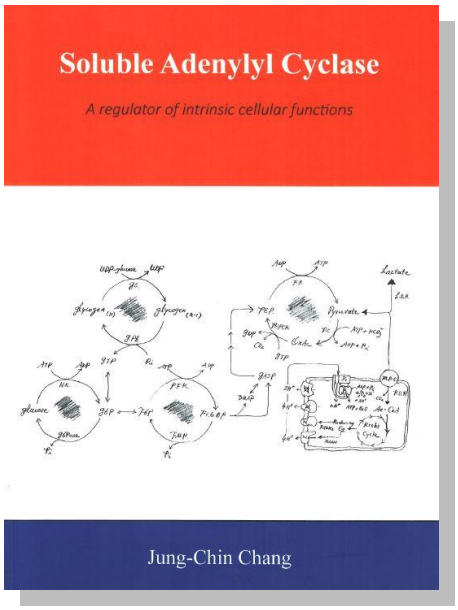

Samenvatting proefschrift J.C. Chang

'Soluble Adenylyl Cyclase — A regulator of intrinsic cellular functions'

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Soluble adenylyl cyclase (sAC, ADCY10) is the latest discovered member of ten mammalian adenylyl cyclases (which make cyclic AMP). Unlike the other adenylyl cyclases, sAC is not localized at the plasma membrane but to various subcellular compartments. sAC activity depends on the cellular ATP level and is stimulated by bicarbonate. The expression of sAC is ubiquitous but particularly high in testes and the epithelial lining of bile duct (cholangiocytes). Its evolutionary conservation and its enzymatic characteristics imply that sAC likely regulates fundamental cellular functions. In this thesis, the role of sAC in apoptosis, glucose metabolism, and bioenergetics is investigated.

Using the immortalized human cholangiocyte H69, I observed upregulation of sAC activity upon down-regulation of the bicarbonate/chloride exchanger AE2, a pathologic hallmark of primary biliary cholangitis (PBC). Down-regulation of AE2 aggravates bile salt-induced apoptosis in cholangiocytes; sAC may play a role in this process as suppression of sAC protects against bile salt-induced apoptosis.

In addition to regulation of apoptosis, I found that sAC regulates the Warburg phenotype, which is found in many tumor cells and characterized by an elevated cytosolic NADH/NAD+ ratio, enhanced glycolytic flux and lactate secretion, and reduced oxidative phosphorylation in multiple tumor cell lines. Remarkably, the reprogramming of cellular bioenergetics by sAC seems to be connected with its regulation of oxidative stress-induced apoptosis. I could show that an increased cytosolic NADH/NAD+ ratio, induced by sAC suppression, protects against oxidative stress-induced apoptosis while a decreased cytosolic NADH/NAD+ ratio sensitizes cells to apoptosis. These data suggest that the cytosolic NADH/NAD+ redox state regulates apoptosis. Further data imply that this occurs by a mechanism involving lysine acetylation and the NAD+-dependent deacetylase SIRT2. Taken together, the present study supports an integrated role of sAC in the regulation of metabolism and apoptosis and establish sAC as a potential therapeutic target in both cholestatic cholangiopathies and anti-cancer therapy.

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