Abstract

Novel crosstalks in Stat3 regulation involving crucial signaling pathways: implications in oncogenesis

Cancer, a group of diseases caused by unregulated cell growth, affects multiple body organs. De-regulation of crucial signaling pathways in cells is thought to be the major reason for cancer initiation and progression. In our work, we studied the regulation of Stat3 signaling in prostate cancer (PCa) and glioblastoma multiforme (GBM).

The work described in this thesis is divided into three main sections. In the first part of the work, the cross-regulation between Stat3 activation and Wnt/β-catenin signaling is investigated. We found that EGFR mediated activation of Stat3 resulted in nuclear accumulation of β-catenin. Conversely, LiCl mediated stabilization of β-catenin resulted in upregulation of Stat3 in PCa. This feedback regulation between two important signaling pathways results in enhanced tumorigenesis.

In the second part, regulation of Stat3 Ser-727 phosphorylation by CK2 was probed. In our study of human glioma patient samples, pStat3\(^{5727}\) was found to occur less frequently when compared to casein kinase 2 (CK2), a kinase involved in cancer progression. In glioma, increased Stat3 Ser-727 phosphorylation was observed upon CK2 inhibition. Stat3 Tyr-705 residue was conversely phosphorylated in similar situations. Though CK2 hyperactivates Akt and Akt is known to mediate Stat3 Ser-727 phosphorylation, Akt mediated regulation of Stat3 Ser-727 was independent of CK2 involvement. Interestingly, protein phosphatase 2A was found to be a mediator in the negative regulation of pStat3\(^{5727}\) by CK2. \textit{In vitro} assays prove that pStat3\(^{5727}\) negatively affects its transcriptional activity. Thus, in gliomas, CK2 may negatively regulate Stat3 Ser-727 phosphorylation thereby enhancing tumorigenicity.

In the last part, we establish the effect of reduced pStat3\(^{5727}\) levels \textit{in vitro} and \textit{in vivo} tumor models. In the \textit{in vitro} system, stable cell lines constitutively expressing Stat3 S727A mutant (Stat3 mut) showed increased rate of cell survival, proliferation and invasion, when compared to either Stat3 WT or empty vector containing cells while rat tumor models injected with the Stat3 mut cells formed more aggressive tumors. Thus, the inhibitory effect of pStat3\(^{5727}\) on Stat3 activation is reduced in Stat3 mut cells thereby leading to more aggressive tumor formation. Targeting Stat3 activity has been the method of choice for therapies against cancer and our study provides novel axes for exploration in this direction.