Beta adrenergic signaling, neuroendocrine differentiation and angiogenesis in prostate cancer progression.

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Background: Treatment-related neuroendocrine prostate cancer (t-NEPC) is an aggressive subtype of prostate cancer (PCa) that is believed to primarily arise through neuroendocrine differentiation (NED) from prostate adenocarcinoma upon resistance to AR pathway inhibitors. With the recent introduction of potent AR pathway inhibitors in clinic, the incidence of t-NEPC is expected to increase substantially. Beta adrenergic signaling (BAS) has been shown to regulate NED, apoptosis and metastasis of PCa cells. BAS also plays a critical role in cancer progression induced by chronic behavioral stress (CBS). However, the molecular mechanisms underlying BAS in PCa progression are still largely unclear.

Methods: In our t-NEPC project, we acquired some t-NEPC cell and xenograft models, and investigated the involvement of several potential key regulators in NED promoted by androgen deprivation treatment (ADT) and by activation of BAS. In our CBS project, we introduced CBS to mice with PCa xenografts through chronic immobilization stress and studied new pathways in angiogenesis and PCa progression though genetic and pharmacological approaches.

Results: In the t-NEPC project, we demonstrated that ADT and BAS activate CREB, which directly targets and induces G protein-coupled receptor kinase 3 (GRK3). GRK3 expression is higher in t-NEPC than in adenocarcinoma, and it positively correlates with CREB activation in human PCa. Overexpressing GRK3 in adenocarcinoma cells induces NE markers. Conversely, silencing GRK3 blocks CREB-induced NED and inhibits proliferation of t-NEPC cells in culture and in tumor xenograft. In the CBS project, we showed that CBS and BAS promote angiogenesis and PCa progression through induction of HDAC2 that in turn epigenetically represses thrombospondin 1 (TSP1), a potent anti-angiogenesis protein. HDAC2 is induced by BAS in vitro and in mouse xenografts, as a direct target of CREB transcriptional activation. Notably, HDAC2 is necessary for BAS to induce angiogenesis of PCa cells.

Conclusions: Our results indicate that GRK3 is a new critical activator of neuroendocrine phenotypes and mediator of CREB activation in promoting NED. Our data also establish a novel pathway of CREB/HDAC2/TSP1 in angiogenesis and PCa progression. Taken together, these two studies provide new insights in BAS in PCa progression and will facilitate the development of novel therapies.

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