

**Stony Brook University
The Graduate School**

Doctoral Defense Announcement

Abstract

**The Fine-Tuning of Receptor Tyrosine Kinase (RTK) Signaling By
Positive and Negative Regulators**

By

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Receptor tyrosine kinases (RTK) are important mediators of signaling pathways leading to the regulation of cell differentiation, proliferation and survival. RTK signaling pathways have been considered as anti-cancer targets since uncontrolled RTK signaling leads to tumorigenesis. To specifically control cellular fate, negative or positive cellular regulators participate in modulating events downstream of RTKs. The goal of this dissertation is to understand how these regulators are controlled and how this is involved in cellular proliferation and survival. One of the negative regulators in RTK mediated signaling is Sprouty (Spry) which was first identified in *Drosophila* as an antagonist of the fibroblast growth factor (FGF) signaling cascade. Recently, the E3 ubiquitin ligase Siah2 has been identified as a negative regulator for hSpry2. In the first part of this study, we aim to characterize how hSpry2 is precisely down regulated by Siah2 upon growth factor stimulation and to determine the functional significance of hSpry2 regulation by Siah2. We have made the interesting discovery that serine phosphorylated forms of hSpry2 are preferential targets for Siah2 and furthermore, the transcriptional level of *Siah2* is also induced by FGF stimulation. This implicates a relationship between Siah2 induction and the temporal regulation of hSpry2 to control FGF signaling.

Ras is a small guanine nucleotide binding protein that connects RTKs to a variety of signaling cascades such as cell growth and differentiation. Ras can transmit signals by cycling between a GDP bound state (inactive) and a GTP bound state (active). The guanine nucleotide exchange factor (GEF) SOS plays a role in activation of Ras by catalyzing the exchange of GDP for GTP. Therefore, we hypothesized that SOS may function as a positive regulator for Ras-induced tumor proliferation. To test this hypothesis, we utilize shRNA targeting human SOS (hSOS) in various human cancer cells and determine whether this knock down has an effect on the cellular proliferation. In this study, we show that the cellular proliferation of most cancer cells is reduced by hSOS knock down even in human cancer cells expressing oncogenic or constitutively active Ras mutation such as pancreatic cancer cells. Therefore, we suggest that SOS may be a key target molecule for designing of anti-cancer therapeutics in human cancers.

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