Title: Alternative splicing and its implication in cancers
Speaker: Dr. Samit Chattopadhyay
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Date: February 18, 2016 (Tue) 14:00-15:30
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Abstract:

Alternative splicing allows a single gene to produce many mRNAs that translates into protein isoforms. More than 95% RNAs go through alternative splicing that has tremendous impact in cancers. We have partly delineated the role of major master regulators involved in the alternative splicing of receptor molecule CD44. The incorporation of the CD44 variable exons confers the metastatic potential to several cancers. We observed that tumor suppressor protein SMAR1 interacts with splicing co-activator SRm160 which is known to regulate Ras dependent CD44 alternative splicing. We found that SMAR1 also interacts with Sam68, another protein of Signal Transducer and Activator of RNA splicing (STAR), allowing MAP kinase mediated activation. We now found an interesting link between the increased expressions of CD44 variables in breast cancer associated with drastic downregulation of SMAR1. Our results unraveled the relation of lower SMAR1 expression and metastatic potential of breast cancer cells. Based on such understanding, we have now designed new molecules that can modulate SMAR1 function which in turn blocks alternative splicing of CD44.

Earlier studies from our lab shown that the levels of SMAR1 in malignant cells are constitutively low, probably because SMAR1 being a tumor suppressor it is essential that a cancerous cell needs to keep it in a suppressed state. Rapidly proliferating cancer cells show significant increase in glycolysis known as the “Warburg effect”. Apart from genotoxic stress another major type of stress which any cell faces is the metabolic stress. As these rapidly proliferating cells have a much higher glucose requirement compared to normal healthy cells, it is really interesting to study the effects of glucose deprivation on these cells. We observe that SMAR1 promoter is controlled by metabolic stress through methylation. Together, dysregulation of tumor suppressor SMAR1 expression is linked to the higher metabolism of cancer cells. Thus, controlling SMAR1 can have therapeutic values against cancers.

This seminar corresponds to "医科学セミナーII、Medical Science Seminar II : Biochemistry and Molecular Biology" in the Master's Program in Medical Sciences (Koji Hisatake) and "医学セミナー、Seminar in Medical Sciences" in the Doctoral Programs in Biomedical Sciences (Chair of Clinical Sciences) and the Doctoral Programs in Clinical Sciences (Shigeru Chiba).

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