REGIONAL CENTRE FOR BIOTECHNOLOGY
Seminar series

Deciphering the Molecular Interplay of Cell Proliferation using *Drosophila*

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Seminar Room

Notch signal activation has been detected in multiple lineages and is responsible for multiple processes during normal development. Overactivation or deregulation of this pathway can lead to cancers such as leukemia. Notch misregulation alone, however, does not appear to be sufficient to cause solid tumors; nevertheless, changes in Notch signaling have been implicated in prostate, breast and other types of cancer. Notch overactivation, which causes a pre-malignant hyper-proliferative state, in concert with mutations in other genes can result in cancerous and even metastatic growth. Since only a few such factors have been identified thus far, we screened the *Drosophila* genome in a systematic manner to identify Notch-synergizing mutations. We identified Myocyte enhancer factor 2 (Mef2), a transcription factor, as a potential candidate for Notch synergies in cancer. Here, we report a novel Mef2-Notch synergy that causes tissue overgrowth and metastatic cell migration in a context independent manner. We observe dramatic overgrowth resulting from increased proliferation of imaginal discs co-overexpressing Notch and Mef2. The invasive marker MMP1 was also upregulated in these discs, and cells expressing Notch and Mef2 together were able to migrate through surrounding tissues. We find that the potent synergy between Mef2 and Notch acts through upregulation of the Jun N-terminal kinase (JNK) pathway, which in turn orchestrates downstream events leading to overgrowth and invasiveness. Introduction of either dominant-negative Basket (the Drosophila JNK homolog) or a mutation in the JNK ligand *eiger* results in rescue of the Notch-Mef2 synergistic phenotype. Finally, we searched for a correlation between Notch and Mef2 expression levels in a panel of gene expression data from human breast cancer samples; we observe a number of strong correlations between specific human Notch and Mef2 family members. These results indicate that the strong synergistic relationship that we observe in *Drosophila* between Notch and Mef2 holds true across species and is likely to be a factor in growth and metastasis of human cancers. 14