SIgN Immunology Seminar

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The many facets of IKKα in the control of tumor development and metastatic progression

Host
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Date
Monday,
8 October 2012

Time
11am – 12pm

Venue
SIgN Seminar Room,
Immunos Building
Level 4
Biopolis

Mammary glands contain luminal and basal epithelial cells, both of which can initiate mammary tumors. Curiously, ErbB2-induced luminal mammary tumors are mainly derived from basal cells. IKKα, activated by NF-κB-inducing kinase (NIK), is important for ErbB2-induced mammary tumorigenesis and tumor-initiating cell (TIC) self-renewal. We now show that the NIK-IKKα module maintains basal, but not luminal, cells in preneoplastic *MMTV-Erbb2* mammary glands. Activated IKK enters the nucleus, phosphorylates p27/Kip1 and stimulates its nuclear export. Reduced p27 expression rescues mammary tumorigenesis in mice deficient in IKKα kinase activity and restores self-renewal of basal type TIC. In human breast cancer, *IKKα* expression shows inverse correlation with metastasis-free survival and presence of nuclear IKKα is linked to decreased nuclear p27 in invasive ductal carcinomas (IDC). We also investigated the role of IKKα in the development, recurrence and metastatic spread of prostate cancer. Just like in breast cancer, IKKα activation is detected in both mouse and human prostate cancer. In mouse models of prostate cancer, IKKα is activated by lymphotoxin (LT) that is produced by B cells that infiltrate the prostate after androgen ablation. Once activated, IKKα accumulates in the nucleus and at the same time, phosphorylates E2F1 and stimulates its nuclear translocation and chromatin recruitment. One of the targets for E2F1 is the Bmi1 gene, whose induction stimulates the proliferation of prostate cancer stem cells, thereby enhancing the recurrence of castration resistant prostate cancer and metastatic spread. An excellent correlation between nuclear IKKα, Bmi1 expression and H2A ubiquitination (a Bmi1-dependent modification) is seen in human prostate cancer. Importantly, the inhibition of IKKα activity acts synergistically with androgen ablation and may represent a novel approach to the therapy of prostate cancer.