東京医学会

東京医学会　第 2583 回集会

日時：平成 24 年 10 月 11 日（木）　18：00〜19：00

場所：東大病院　入院棟 15 階　大会議室

演者：Harold L. Moses 博士

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演題：TGF-ß Regulation of Chemokine Expression and Metastasis: Therapeutic Implications

要旨：　Harold Moses 博士は TGF-β 研究を牽引する著名な研究者であり、本セミナーでは TGF-β によるケモカイン発現を介したがん微小環境の制御機構についてご講演いただきます。

Accumulating data indicate that an inflammatory microenvironment can play a critical role in cancer initiation and progression. TGF-ß signaling in both epithelial and stromal cells appears to be a key regulator of this microenvironment. There is now compelling evidence from transgenic mouse studies and analyses of mutations in human carcinomas indicating that the TGF-ß signal transduction pathway is tumor suppressive. However, there is evidence that TGF-ß signaling can promote tumor progression in the later stages. In order to examine the roles of TGF-ß signaling in cancer more closely, we have generated mice with *loxP* sites flanking exon 2 of the type II receptor gene, *Tgfbr2*, and crossed them with mice expressing Cre driven by different epithelial specific promoters in the mammary gland and pancreas. Loss of TGF-ß signaling gave a minimal phenotype. However, when challenged with oncogene expression, there was rapid development of invasive and metastatic carcinomas. In an effort to address mechanisms, we have now identified gene expression signatures associated with the TGF-ß signaling pathway in mammary carcinoma cells. The results strongly suggest that TGF-ß signaling mediates intrinsic, stromal-epithelial and host-tumor interactions during breast cancer progression, at least in part, by regulating induced *Cxcl1*, *Cxcl5* and *Ccl20* chemokine expression. To determine the clinical relevance of our results, we queried our TGF-ß associated gene expression signatures in four human breast cancer data sets containing a total of 1,319 gene expression profiles and associated clinical outcome data. The signature representing complete abrogation of TGF-ß signaling correlated with reduced relapse-free survival in all patients, particularly in patients with estrogen receptor positive tumors. The functional significance of increased chemokine expression in the knockout carcinoma cells in the mouse model is recruitment of immature bone marrow derived cells that express abundant TGF-ß and MMPs in the tumor microenvironment and promote invasion and metastasis in part through matrix alterations. The data indicate that TGF-ß signaling is a major regulator of chemokine secretion and resultant myeloid cell infiltration modulating the inflammatory microenvironment. Preclinical data indicate that blocking chemokine signaling can have therapeutic benefit.

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