Cancer Science Institute of Singapore
Research Meeting

Date: Friday, 24 April 2015
Time: 12pm – 1pm
Venue: LT 36, Level 3 Auditorium, MD6
14 Medical Drive, Singapore 117599

Vijay Pandey
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Expression of two genetic elements is sufficient to stimulate oncogenic transformation of human mammary epithelial cells

Cell proliferation and survival have been postulated to provide a platform for oncogenic transformation of normal cells and which may occur through the constitutive activation of growth promoting factors and their downstream effectors. TFF3 has been reported to stimulate tumor progression and metastatic seeding of ER+ MC cells. However, the functional role of TFF3 in oncogenic transformation largely unknown. We observed that simple forced expression of TFF3 efficaciously stimulated oncogenic transformation of *immortalized* but otherwise normal HMECs. Forced expression of TFF3 in *immortalized*-HMECs enhanced cell proliferation, cell survival, anchorage independent growth and produced highly disorganized three-dimensional (3D) acinar structures; and importantly generated tumours in nude mice. Forced expression of TFF3 in *immortalized*-HMECs stimulated STAT3 activity that was required for TFF3-stimulated cell proliferation and survival, and anchorage independent growth. TFF3 specifically utilized STAT3 activity to govern a transcriptional program, which was required for TFF3-stimulated oncogenic transformation of *immortalized*-HMECs including transcriptional up-regulation of proto-oncogenes, *CCND1* and *BCL2*. *siRNA*-mediated depletion or functional inhibition of STAT3 significantly inhibited the TFF3-stimulated transcription of *CCND1* and *BCL2* , and oncogenicity in *immortalized*-HMECs. Furthermore, DOX-induced expression of TFF3 in HMEC-*hTERT* cells also produced highly disorganized 3D acinar structures in Matrigel culture. Removal of DOX-induced expression of TFF3 in HMEC-*hTERT* cells, previously grown with DOX resulted in efficient normalization of the disorganized 3D acinar architecture in Matrigel. Thus, TFF3 is potent oncogene and utilizes STAT3 signaling to execute its oncogenic transforming activity in *immortalized*-HMECs. This study therefore provides evidence that the expression of two non-mutated genetic elements is sufficient to produce oncogenic transformation of HMECs.

Sheng Wanqiang
Research Fellow, Prof. Xin-Yuan Fu's Group

STAT5 programs a distinct subset of GM-CSF-producing T helper cells that is essential for autoimmune neuroinflammation

In response to antigenic assault, naïve CD4+ T cells differentiate into various subsets of effector T helper (TH) cells with differential cytokine production and distinct functions. STAT proteins transmit inflammatory cytokine signals which crucially direct the differentiation of antigen-specific CD4+ T cells by inducing the expression of subset-specific transcription factors. STAT5 transmits IL-2 signals and is crucial for Treg development , but also negatively regulates TH17 differentiation. However, its function in T cell-mediated autoimmune diseases has not been well documented. In this study, surprisingly, we found STAT5 was indispensible for the encephalitogenicity of autoreactive CD4+ T cells in EAE. Further investigation showed that IL-7-STAT5 signaling induced optimal GM-CSF production in pathogenic CD4+ T cells, which was important for inducing effective neuroinflammation. In vitro studies showed that GM-CSF-producing CD4+ T cells regulated by IL-7-STAT5 signaling may represent a new TH subset with a distinct differentiation program and cytokine production profile. Our preliminary data also suggest that this subset of TH cells might also be involved in regulating tumour metastasis.