SIgN Immunology Seminar



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Mouse dendritic cell maturation and cancer stem cell maintenance, two different scenarios same player: Toll-like receptors-2

Host
Dr Francesca Zolezzi
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Date
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Time
3pm – 4pm

Venue
SIgN Seminar Room,
Immunos Building
Level 4
Biopolis

The protein encoded by toll-like receptor 2 (TLR2) gene is a member of the Toll-like receptor (TLR) family, which plays a fundamental role in pathogen recognition and activation of innate immunity. In this report we present two different scenarios in which TLR plays a pivotal role: cancer stem cells (CSCs) maintenance and dendritic cells maturation.

CSCs are responsible for tumor progression, metastasis, resistance to therapy, and tumor recurrence. Transcription profiling of a tumor cell line versus its derived, CSC-enriched mammospheres indicated TLR2 expression in tumor cells and preferentially in CSCs. TLR2-signaling inhibition strongly impaired, in vitro, mammospheres generation from murine and human cell lines. Similar results were obtained by inhibiting the endogenous TLR2-ligand HMGB1. TLR2 inhibition also resulted in a decrease in mammosphere tumorigenicity and metastatic ability. Collectively these results demonstrate that TLR2 and its endogenous HMGB1 regulate CSCs self-renewal.

Lactoferrin, a key component of innate immunity, is a cationic monomeric 80 kDa glycoprotein of the transferrin superfamily. Recombinant human lactoferrin, known as talactoferrin (TLF), induces a distinct functional maturation program in human dendritic cells (DC) derived from peripheral blood monocytes. However, the receptors and molecular mechanisms involved in this induction have not been fully determined. By exploiting genome-wide transcription profiling of immature, TNFα/IL1β-matured DC (m-DC), and TLF-matured DC (TLF-DC), we have detected a set of transcripts specific for m-DC and one specific for TLF-DC. Functional network reconstruction highlighted, as expected, the association of m-DC maturation with IL-1β, TNF-αα and NF-κB, whereas TLF-DC maturation was associated with ERK and NF-kB. This involvement of ERK and NF-κB transduction factors suggests direct involvement of TLR in TLF-induced maturation. We have used MyD88 inhibition and siRNA silencing TLR on human DCs, and mice TLR-2 KO and TLR-2/TLR-4 double KO, to show that TLF triggers the maturation of both human and mouse DC through TLR-2 and TLR-4.