SIgN Immunology Seminar

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The role of IL-12 as a tumor suppressor and its impact on innate and adaptive immunity

Host
Dr Paola Castagnoli
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Date
Tuesday, 10 July 2012

Time
11am – 12pm

Venue
SIgN Seminar Room,
Immunos Building
Level 4
Biopolis

The cytokine Interleukin-12 (IL-12) has been demonstrated to have potent tumoricidal activity in a variety of preclinical models of cancer but also in clinical trials in humans. In patients, systemic administration leads however to severe adverse effects hampering its clinical development. Our primary interest was to determine the *modus operandi* of IL-12 as an anti-tumor immune stimulant. We used models of glioblastoma and melanoma in mice to study how IL-12 suppresses and/or eradicates tumors. IL-12 is widely held to activate and polarize natural killer (NK) and type 1 T helper (TH1) cells.

By systematic analysis of the immune response to an Interleukin-12 secreting melanoma cell line (B16) we found that tumor suppression is mediated independently of T lymphocytes or natural killer cells. We discovered that Interleukin-12 initiates powerful local anti-tumor immunity by stimulating a subset of innate lymphocytes (ILCs) dependent on the transcription factor RoRγt. The presence of these ILCs leads to the upregulation of adhesion molecules in the tumor vasculature and increased leukocyte invasion. These findings clearly attribute a novel function to this only recently identified cell type in tumor immunology.

Conversely, we found that the formation of melanoma metastasis in the lung is entirely dependent on the activity of conventional NK cells. Yet, when studying the impact of IL-12 on glioblastoma growth in the brain, we were surprised to find that here, IL-12 triggers potent T cell immunity and leads to the establishment of long lasting anti-tumor memory. This finding permits is to combine IL-12 and blockage of co-inhibitory signals (such as PDL1 or CTLA-4) to treat brain tumors and we are initiating a clinical trial at our Neurooncology unit to treat refractory glioblastoma patients.

Taken together, we propose that IL-12 possesses not only potent anti-tumor activities, but that its impact on different lymphocyte populations depends entirely on the tumor-bearing organ.