SIgN Immunology Seminar

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Generation of immune-privileged pre-metastatic niches by primary tumour hypoxia

Host
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Date
Monday
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Time
11am – 12pm

Venue
SIgN Seminar Room
Immunos Building
Level 4
Biopolis

Hypoxia is a common feature and poor prognostic factor in many solid cancers. Within the primary tumour, hypoxia acts as a strong selective pressure that promotes angiogenesis, invasion and metastatic spread of cancer cells. Metastasis is the most common cause of mortality in cancer patients. While tumour cell-intrinsic mechanisms promoting metastasis are beginning to be understood, the contribution of the stroma at metastatic sites is less well defined. We and others have shown that pro-tumourigenic properties of future metastatic sites are determined by the interactions between factors secreted by the primary tumour and bone marrow-derived immune cells, which drives formation of permissive environments, called pre-metastatic niches. These are established before the arrival of tumour cells.

In this presentation, it will demonstrated, that in different immune competent, syngeneic cancer models, primary tumour hypoxia promotes pre-metastatic niche formation. Cell-free supernatant derived from breast tumour cells results in increased bone marrow-derived cell infiltration into the lungs, and leads to increased metastatic burden in experimental metastasis models, suggesting reduced immune surveillance in pre-metastatic niches.

We define bone marrow-derived CD11b+/Ly6Cmed/Ly6G+ myeloid and CD3-/NK1.1+ NK cell lineages as main constituents of the pre-metastatic niche, and show that NK cell cytotoxicity and maturity is decreased. The CD11b+/Ly6Cmed/Ly6G+ population is defined as a granulocytic subset of myeloid cells with increased pSTAT3 and CCR2 expression, whose mobilization and recruitment to the pre-metastatic niche is controlled by secretion of the soluble factor MCP-1/CCL2 from hypoxic breast cancer cells. Furthermore, we identify tumour hypoxia to cause the increased secretion of exosome by cancer cells. We define the protein and RNA content of these exosomes in an unbiased manner, and investigate their capacity to generate pre-metastatic niches. Furthermore, the possibility of using the unique protein and RNA content of exosomes as novel diagnostic signatures and therapeutic targets for the prevention of metastasis in cancer patients will be addressed.