Symposium D

Chemokines and cell trafficking

SD-1

NEW SIGNALS TO DIRECT DENDRITIC CELL TRAFFICKING

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Dendritic cells (DC) are professional antigen presenting cells that play a pivotal role in the activation of adaptive immunity. Tissue invasion by pathogens induces the recruitment of blood DC to the site of infection and promote their subsequent migration to secondary lymphoid organs. This complex process relies on the expression and regulation of chemotactic receptors on the surface of migrating DC and on the activation of adhesion molecules that allow DC to properly interact with both blood and lymphatic vessels. In the absence of correct tissue localization, DC fail to promote proper immune responses. Recent work has documented that in addition to chemokines, a number of nonchemokine chemotactic factors play a crucial role in DC accumulation to pathological tissues. In addition, several agonists devoid of chemotactic activity are known to regulate DC migration to peripheral inflammatory tissues and to regional secondary lymphoid organs. These concepts will be reviewed in the context of recent acquisitions about the action of new lipid signals involved in the migration of maturing DC to lymph nodes. Furthermore, we will provide evidence for the role of a new chemotactic receptor in the trafficking of lung DC in vivo in a murine asthma model.

SD-2

REGULATION OF THE INFLAMMATORY RESPONSE BY THE CHEMOKINE RECEPTOR D6

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The chemokine receptor D6 is a highly atypical chemokine biding protein. It is promiscuous and binds all inflammatory CC chemokines but not constitutive CC chemokines. It is expressed by lymphatic endothelial cells in the skin, gut and lung. Previous in vitro work has indicated a role for D6 as a 'decoy' receptor which internalises and degrades chemokines with remarkable efficiency. To analyse the roles for D6 in vivo, we have generated D6-null mice. We have examined the response of these mice in models of cutaneous inflammation. Specifically we have used the phorbol ester, TPA, to induce cutaneous inflammation. In the wild type mice, treatment with TPA induces a transient inflammatory response that is rapidly resolved. In contrast, in the D6-null mice, TPA induces a much more exaggerated inflammatory response and the mice develop a severe cutaneous inflammatory pathology that has many similarities to human psoriasis. Biochemical analyses indicate that the development of this pathology correlates with an inability of the D6 null mice to effectively clear inflammatory CC chemokines from the inflamed skin. The inflammatory pathology that develops is T cell and mast cell dependent and can be blocked with antibodies to TNFalpha. Thus our in vivo studies indicate that D6 regulates the post inflammatory clearance of inflammatory Chemokines from cutaneous sites and therefore contributes in a novel way to the overall orchestration of the inflammatory response. In the absence of D6 the reduced clearance of chemokines from the skin results in the induction of a marked psoriasiform pathology. Most recently we have been examining the susceptibility of the D6 null mice to skin tumour formation. In accordance with the enhanced inflammation seen in these mice, they display a much increased susceptibility to skin tumour formation. Intriguingly, this can be reversed by transgenic expression of D6 within the epidermis.

SD-3

NOVEL INSIGHTS INTO THE MECHANISMS LEADING TO THE FORMATION OF TERTIARY LYMPHOID STRUCTURES IN THE THYROID GLAND

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The formation of lymphoid structures in the non-lymphoid tissues is a hallmark of autoimmune inflammatory diseases such as rheumatoid arthritis and Hashimoto's thyroiditis. Transgenic expression of the chemokine CCL21, which is expressed in the thyroid of patients with autoimmune thyroiditis, leads to the formation of lymphoid structures in the thyroid, indicating a critical role for this molecule in the formation of tertiary lymphoid aggregates. Lymphoid structures observed in the thyroid of TGCCL21 mice are indistinguishable of tertiary lymphoid tissue, as they contain segregated T and B lymphocytes, large number of dendritic cells, organized FDC clusters and specialized vascular structures. Our results indicate that formation of lymphoid structures does not depend on conventional LTi cells as they develop in mice that lack Id2, a transcription regulator that is critical for differentiation of conventional LTi cells. Rather, mature $CD3^+CD4^+$ T cells were critical for the development of tertiary lymphoid structures. The initial stages of this process involved interaction of $CD3^+CD4^+$ T cells with dendritic cells (DC), the appearance of $PNAd^+$ vessels and production of chemokines that recruit lymphocytes and DC. These findings indicate that the formation of tertiary lymphoid structures does not require Id2-dependent conventional LTis, but depends on a program initiated by mature $CD3^+CD4^+$ T cells.