PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Getting under your skin: dendritic cells and autoimmunity

ArticleInfo		
ArticleID	:	55
ArticleDOI	:	10.1186/ar-2001-71201
ArticleCitationID	:	71201
ArticleSequenceNumber	:	12
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	3
ArticleHistory	:	RegistrationDate : 2001–9–13 Received : 2001–9–13 Accepted : 2001–10–4 OnlineDate : 2001–10–4
ArticleCopyright	:	Biomed Central Ltd2001
ArticleGrants	:	

ArticleContext	:	130753311

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Keywords

Autoimmunity, CD40 ligand, Langerhans cell

Context

CD40 ligand (CD154), a soluble member of the tumor necrosis factor family of cytokines, is expressed on the cell surface of activated CD4 T lymphocytes in a controlled manner. CD154 is critical for the activation of antigen-presenting cells, such as dendritic cells (DCs) and B cells, through interaction with its receptor, CD40. CD154 stimulation of B cells is required for B-cell differentiation and immunoglobulin class switching. In humans, lack of expression of CD154 leads to profound immunodeficiency, conversely, overexpression is seen in autoimmune disorders such as systemic lupus erythematosus and systemic sclerosis.

Significant findings

Using a keratinocyte-specific promoter to express CD154 as a transgene in the skin of mice, Mehling and co-workers produced a spontaneous model of systemic autoimmunity. Of these transgenic animals, 80% developed dermatitis by 1.5 months of age. Lymphadenopathy was localized to draining nodes from the skin; these nodes contained increased numbers of B cells and activated DCs. Histopathology revealed decreased numbers of Langerhans cells (LCs)-specialized skin DCs-in the epidermis, yet increased numbers in the dermis suggesting translocation. Skin painting confirmed $CD11c^{+}$ LCs migrated from the skin to enlarged draining nodes. Decreased serum IgM and increased IgG1, IgG2, and IgE were noted, consistent with CD154 stimulation of B cells. Correlatively, the mice exhibited autoantibody deposits in the kidneys. Proteinuria and lung fibrosis were noted, and the mice died prematurely. Lastly, adoptive transfer of CD8 T cells from the CD154 transgenics was capable of transferring dermatitis to wild-type recipient animals.

Comments

This manuscript showed forced expression of CD154 in the skin activated resident LCs/DCs leading to autoimmunity. Whether this particular mouse is a model for mixed connective tissue disease (MCTD) versus a more generalized autoimmunity is unclear. However, several features of MCTD, including autoantibodies, kidney, skin, and lung involvement were present. Interestingly, no arthritis developed. Because CD154 was overexpressed in the skin, the activated DCs may not migrate to the joint. Intriguingly, CD8 T cells, but not CD4 T cells or serum, were capable of transferring dermatitis; whether CD8 T cells can transfer systemic manifestations is unknown. It was surprising that no deviation in cytokine expression patterns was noted as CD154 expression is often linked to induction of a Th1 cytokine profile. Although suggested, no direct evidence for loss of tolerance to autoantigens was demonstrated.

Methods

Transgenic mice, histopathology, flow cytometry, adoptive transfer, ELISA

Additional information

References

1. Mehling A, Loser K, Varga G, Metze D, Luger TA, Schwarz T, Grabbe S, Beissert S.: Overexpression of CD40 ligand in murine epidermis results in chronic skin inflammation and systemic autoimmunity. J Exp Med . 2001, 194: 615-628.