Thymus **13**: 201–204, 1989.

Control of lymphoepithelial interactions within thymic nurse cells by gamma-interferon and tumor necrosis factor alpha

Possible role in the modulation of intrathymic education?

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Key words: gamma interferon, thymic nurse cells, tumor necrosis factor

Abstract. The role of cytokines in the process of intrathymic differentiation is not yet clearly established. The results presented in this paper demonstrate that interferon-γ and tumor necrosis factor-α regulate 'in vivo' and 'in vitro' the interactions between epithelial cells and thymocytes within thymic nurse cells. The mechanism of action of these cytokines and their possible physiologic role 'in vivo' are discussed.

Abbreviations: IFN-γ: gamma-interferon; MHC: major histocompatibility complex; TNC: thymic nurse cell; TNF-α: tumor necrosis factor-alpha.

Introduction and discussion

The thymus plays a crucial role in the development of T lymphocytes. Bone marrow precursors enter this organ and, under the influence of its microenvironment, are triggered to proliferate, to differentiate, to rearrange their T-cell receptor genes and to mature into functional T lymphocytes that show major histocompatibility complex (MHC) restriction and tolerance to self [1, 2, 3].

The respective role of direct contact of the precursor cells with the cells which constitute the thymic microenvironment and of the soluble factors produced within the thymus is not yet clearly established although both are thought to represent necessary steps in T cell maturation [4].

The role of cytokines in particular is presently a matter of extensive investigations. Several experiments clearly indicate that subsets of thymic cells are able to produce various kinds of cytokines whereas other cells might be triggered to proliferate and/or to differentiate under their influence [5, 6,

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7]. These observations have elicited research attempting to elucidate their involvement in T-cell development.

Among the presently studied cytokines, interferon-γ (IFN-γ) and tumor necrosis factor α (TNF-α) may play an important role. These cytokines are produced within the thymus: activated thymocytes release IFN-γ 'in vitro' [8] and traces of IFN-γ activity have been found in supernatants of early thymic cultures [7]. It has also been recently shown that thymic cells located at the cortico-medullary junction, probably accessory cells, produce TNF-α (O. Stutman; personal communication).

The present paper deals with the effects of these cytokines on the interactions between lymphocytes and epithelial cells within thymic nurse cells (TNC). Repeated injections of these factors in normal young adult mice increase the numbers of TNC which are recovered from thymuses. They stimulate TNC-derived epithelial cells to establish interactions with thymocytes 'in vitro' and to form new lymphoepithelial complexes. They are also able to induce the recovery of this property in altered TNC-derived epithelial cells that are unable to reassociate with normal thymocytes, as observed with epithelial cells collected from prelymphomatous thymuses after a leukemogenic split dose irradiation [9]. This indicates that IFN-γ and TNF-α act as regulators of one function of thymic cortical epithelial cells.

What is the mechanism of action of these cytokines on epithelial cells? – IFN-γ is known to modulate 'in vitro' the expression of Ia molecules at the surface of several cell types including thymic accessory cells [7] and thymic epithelial cells [10, 11]. A similar effect can take place in the whole thymus: it was demonstrated that adding macrophages and/or dendritic cells into cultured fetal thymus lobes causes a marked rise in the density of endogenous Ia molecules expressed on epithelial cells in the cortex. These effects were inhibited by adding anti-IFN-γ monoclonal antibodies [11]. To our knowledge, the effects of TNF-α upon thymic stromal cells have not yet been investigated, nevertheless it can also increase the expression of class II MHC molecules at the surface of several cell types [12]. IFN-γ and TNF-α might thus control the intra-TNC lymphoepithelial interactions via the regulation of Ia molecule expression. One can thus postulate that activation of thymocytes or macrophages 'in vivo' might lead to an intra-thymic physiologic release of IFN-γ and/or TNF-α which then act on epithelial cells and therefore on the lymphoepithelial interactions responsible for the formation of TNC. The signals responsible for this intrathymic cytokine production have still to be studied.

Finally, one might postulate that IFN-γ and TNF-α thus participate in the control of intrathymic selection, through the activation of the lymphoepithelial interactions. Indeed, almost all theories that account for positive selection invoke reaction of receptors of thymocytes with MHC molecules

on thymic cortical epithelial cells [13]. Moreover, it has been recently shown that epithelial TNC could also be involved in negative selection since they are able to present self-antigens complexed with MHC molecules [14]. Macrophages and dendritic cells would thus be implicated in the control of thymic selection not only by themselves, though the expression of MHC molecules on their membrane, but also by maintaining functional levels of Ia expression on cortical epithelial cells, though cytokine release.

Acknowledgments

We thank Boehringer-Ingelheim for providing IFN-γ and TNF-α. Besides, this work was supported by the Fund for Medical Scientific Research and the Centre Anticancereux pres l'Université de Liège.

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