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RESEARCH

Decreased Interferon γ Production in $CD3^+$ and $CD3^-CD56^+$ Lymphocyte Subsets in Metastatic Regional Lymph Nodes of Melanoma Patients

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Abstract As lymphogenic dissemination is very common in melanoma, regional lymph nodes (LN)s represent first immunological barriers to tumor invasion and play a complex role in antitumor immune defense. In this sense, their most prominent role is the presentation of tumor-derived antigens to naïve T cells and generation of cell-mediated adaptive immune response. Since tumor micro-environment affects immune cell function in this study we have evaluated the ability of T cells and NK cells in metastatic (involved) and non-metastatic regional LNs to produce interferon γ (IFNγ), a pleiotropic cytokine that regulates adaptive antitumor immune response. Our results show reduced IFNγ production in both T and NK lymphocyte subsets and decreased prevalence of T cells in metastatic regional LNs of melanoma patients. The decrease of IFNγ production in T cells was more pronounced with increased number of involved regional LNs indicating tumor-induced functional impairment of both T and NK cell lymphocyte subsets in involved regional LNs. Therefore, shown low IFNγ production in metastatic LNs may represent an obstacle in adaptive cell-mediated antitumor immune response and hence may enable tumor progression.

Keywords Regional lymph nodes · Interferon γ · T cells · NK cells

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Introduction

As lymphogenic dissemination is the most common in melanoma, regional lymph nodes (LN)s represent the first immunological barrier for spreading this tumor into visceral organs. Among many complex roles of regional LNs in antitumor immunity the most prominent one is the presentation of tumor-derived antigens to naïve T cells and generation of adaptive immune response [1].

Interferon (IFN)γ is a type II interferon and its biological activity is associated with antitumor mechanisms during cell-mediated adaptive immune responses. The most prominent role of IFNγ in upregulation of major histocompatibility complex class I (MHC I) molecule expression that aids the priming and presentation of antigens by antigen presenting cells (APC)s [2]. IFNγ is as a pleiotropic cytokine involved in differentiation and regulation of function of many immune cell types. In this sense IFNγ stimulates Th-1, while inhibits Th2 T cell responses, activates macrophages and induces production of chemokines which recruit specific effector cells to the site of inflammation. IFNγ is produced mainly by $CD4^+$ T helper cell type 1 (Th1) lymphocytes, $CD8^+$ cytotoxic T lymphocytes (CTL)s and natural killer (NK) cells [3]. Both T and NK cells have been found to co-localize in T cell-dependent paracortical area of LN where naïve T cells are brought into contact with APCs [4]. Dendritic cells (DC)s are the most prominent APCs that patrol peripheral sites and upon tumor antigen-induced maturation migrate to draining LNs [5]. Mature DCs in LNs present tumor antigens and prime both $CD8^+$ and $CD4^+$ T cell responses, secrete interleukin (IL)-12 and IL-15 and subsequently activate NK cells [6]. In LNs activated NK cells by secreting IFNγ assist in Th1 polarization in DC-mediated T cell priming. Th1 polarized $CD4^+$ T cells exert antitumor response *via* both IFNγ and IL-2 secretion [7, 8] and provide helper signals to CTL-mediated cytolysis of

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