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Short communication

Membrane-Bound Tumour Factors Limiting NK-Mediated Immune

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DESCRIPTION

Many evidences suggest that NK cells are effective in patrolling for and eliminating tumors in their onset phase, but hardly limit the progression of large established solid tumors. Beside the transition of tumor cells towards a more aggressive phenotype, the NK cell efficacy might be limited by a complex immunosuppressive milieu present in the tumor microenvironment. Indeed, different mechanisms damping NK cell function have been shown in these last years. These include a plethora of tumor-derived immunomodulatory soluble factors (TGF-β, MIF, adenosine, L-Kynurenin, PGE2) as well as soluble ligands (MICA, ULBP-2, PVR, B7-H6) that compete with membrane-bound tumor ligands for binding to activating NK receptors. During NK-tumor cell contact the NK cell function can also be inhibited by the engagement on NK cells of different inhibitory receptors. The specific ligands might be either constitutively expressed at the tumor cell surface (HLA-I, B7-H3, PVR) or de novo induced/up-regulated (PD-Ls) by immune stimulatory factors (IFN-γ, TNF-α). These are largely released during the active phases of the immune responses and exert an unwanted side effect called "tumor adaptive immune resistance". This review aims to summarize the best-known molecular mechanisms that, at various times and in different ways, can limit the efficacy of the NK-mediated immune surveillance of tumors.

Keywords: Immune; Tumor; Immunomodulatory

DISCUSSION

Natural killer cells (NK) are crucial cytolysis effectors belonging to the family of innate lymphoid cell (ILC) [1,2]. Originally described as cells exerting a "natural" catalytic activity due to their capability to kill the highly susceptible K562 eritroleukemia cell line, it is now well established that they require activation to exert optimal effector functions. Moreover, the susceptibility to NK-mediated killing of established tumor cell lines is superior to that of tumors ex-vivo isolated from patients, as occurs in bone marrow metastases that are much more resistant to NK-mediated aggression [3]. This supports the concept that an effective NK-mediated anti-cancer activity can't dispense with an optimal activation of endogenous or adoptively transferred NK cells. It is also crucial to understand which NK cell subset, once activated, can exert the most effective anti-cancer activity in a particular immunotherapeutic setting. Indeed, it has been recently stressed that a great heterogeneity in NK cell phenotype and functions exists that goes beyond the classical CD56dim CD16high and CD56brightCD16low/neg NK cell dichotomy [4]. Beside the identification and description of CD56neg NK cells [5] that are particularly abundant in peripheral blood of virus-infected donors, several studies highlighted the great heterogeneity of peripheral blood CD56dim NK cells, which include subpopulations characterized by different capabilities of being activated by cytokines, antibodies or tumor contact [6,7].

CONCLUSION

NK cell-based immunotherapy is becoming a promising approach for the treatment of both haematological malignance's and solid tumors. However, recent published data show that the complexity of the immune-suppressive milieu characterizing the tumor microenvironment can't be neglected. Indeed, different inhibitory mechanisms represented by soluble factors or by tumor-associated surface ligands could deeply reduce the NK cell activity against tumors. Importantly, malignant cells can constitutively express some of these ligands (HLA-I, B7-H3) or increase/de novo induce their expression (PD-Ls) as an adaptive defence mechanism promoted by immune stimulatory factors (IFN-γ) that are released during effective NK and TH1 cell-mediated immune responses. Thus, future immunotherapeutic interventions should consider the possible onset in patients of multiple, different immunosuppressive mechanisms affecting the function of endogenous or adoptively transferred NK cells. Also the chemokine receptor repertoire acquired by NK cells during their in vitro-expansion needed for the adoptive transfer inpatients should not be neglected. Along this line, it might be relevant to hinder the effects of factors (TGF-β 1) capable of modifying, in endogenous or infused NK cells, the expression of chemokine receptors crucial for their extravasation and recruitment at the tumor sites.

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