IJAE
Vol. 121, n. 1 (Supplement): 23, 2016
ITALIAN JOURNAL OF ANATOMY AND EMBRYOLOGY

Identification of a subset of human Natural Killer cells expressing high levels of Programmed Death 1: A phenotypic and functional characterization

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Background: PD-1 is an immunological checkpoint that limits immune responses by delivering potent inhibitory signals to T cells upon interaction with specific ligands expressed on tumor/virus-infected cells, thus contributing to immune escape mechanisms (1). Therapeutic PD-1 blockade has been shown to mediate tumor eradication with impressive clinical results. Little is known on the expression/function of PD-1 on human NK cells (2). Objective: To clarify whether human NK cells may express PD-1 and analyze their phenotypic/functional features. Methods: Multiparametric cytofluorimetric analysis of PD-1+ NK cells and their functional characterization by degranulation, cytokine production and proliferation assays. Results: We provide unequivocal evidence that PD-1 is highly expressed (PD-1bright) on a NK cell subset detectable in the peripheral blood of approximately one fourth of healthy individuals. These donors are always serologically positive for HCMV. PD-1 is expressed by CD56dim but not by CD56bright NK cells and is confined to fully mature NK cells characterized by the NKG2A-KIR+CD57+ phenotype. The proportions of PD-1bright NK cells were higher in the ascites of a cohort of ovarian-carcinoma patients suggesting their possible induction/expansion in tumor environments. Functional analysis revealed a reduced proliferative capability in response to cytokines, low degranulation and impaired cytokine production upon interaction with tumor targets. Conclusions: We have identified and characterized a novel subpopulation of human NK cells expressing high levels of PD-1. These cells have the phenotypic characteristics of fully mature NK cells and are increased in ovarian-carcinoma patients. They display low proliferative responses and impaired anti-tumor activity that can be partially restored by antibody-mediated disruption of PD-1/PD-L interaction.

This work was supported by grants awarded by Associazione Italiana per la Ricerca sul Cancro-(AIRC-) Special Project 5x1000 no. 9962 and AIRC-IG 2014 Id. 15704 (Alessandro Moretta), AIRC-IG 2014 Id. 15283 (Lorenzo Moretta), Progetto di Ricerca di Ateneo 2014 (Emanuela Marcenaro) and Olive Daniel laboratory is supported by the Fondation pour la Recherche Médicale (Equipe FRM DEQ20140329534).

References

[1] Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol 2008; 26: 677-704.

[2] Okazaki T, Chikuma S, Iwai Y, Fagarasan S, Honjo T. A rheostat for immune responses: the unique properties of PD-1 and their advantages for clinical application. Nat Immunol 2013 Dec; 14(12):1212-8.

Keywords

Natural Killer cells; programmed death receptor (PD-1); ovarian carcinoma; tumor escape; immune checkpoint; NK cell degranulation; NK cell proliferation; NK cell cytokine production; CD57+ NK cells; CMV.