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Continuous stress disrupts immunostimulatory effects of IL-12

Ben Levi, Marganit Benish, Yael Goldfarb, Liat Sorski, Rivka Melamed, Ella Rosenne, Shamgar Ben-Eliyahu *

Neuroimmunology Research Unit, Department of Psychology, Tel-Aviv University, Tel-Aviv 69978, Israel

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ABSTRACT

Immune stimulation by biological response modifiers is a common approach in tumor immunotherapy. IL-12 was found effective in various animal studies, but clinical trials showed limited success. However, among other differences, animal models do not simulate psychological or physiological stress while employing IL-12, whereas cancer patients often experience distress while treated with immunostimulants. Thus, in the current study we assessed the impact of continuous stress on the efficacy of IL-12 immunostimulation. F344 rats were subjected to a pharmacological stress paradigm (continuous administration of a β-adrenergic agonist) or to a 20 h behavioral stress paradigm (wet cage exposure) commencing 2 h before IL-12 administration. Twenty-six hours after stress initiation, we studied indices known to reflect IL-12 immunostimulatory impacts, including NK cell numbers and activity in different immune compartments, and *in vivo* resistance to MADB106 lung tumor colonization. The results indicated that both the pharmacological and behavioral stress paradigms significantly reduced the increase in the number and activity of marginating-pulmonary NK cells evident in non-stressed IL-12 treated animals. Additionally, stressed animals exhibited a lower IL-12-induced improvement of MADB106 lung clearance, an *in vivo* index that markedly depends on total marginating-pulmonary NK activity. These deleterious effects of stress were more prominent in males than in females. Overall, the findings demonstrate that prolonged stress exposure can disrupt the efficacy of simultaneous immunostimulatory treatments, irrespective of stress effects on baseline immune measures. Neuroendocrine and cellular mediating mechanisms are yet unknown, but the potential clinical ramifications of these findings warrant consideration in clinical trials employing immunostimulatory agents.

1. Introduction

Immune stimulation by cytokines or other biological response modifiers (BRMs) is a common approach in the field of tumor immunotherapy. The use of type 1 T-helper (T_H1) and proinflammatory cytokines (e.g. IL-12, IL-2, IFN-γ) was shown to significantly improve T_H1-dependent cellular immunity (Smyth et al., 2004), which is known to play a crucial role in the *in vivo* eradication of tumor cells (Nishimura et al., 2000).

IL-12 is one of the vastly investigated cytokines in this context, being a major T_H1 differentiation and cellular immunity inducer. Its ligation to the IL-12 receptor (IL-12R), primarily expressed by activated T and natural killer (NK) cells (Desai et al., 1992), results in a signal transduction that activates STAT4, which was reported to mediate most of IL-12's biological activities through the production of IFN-γ (Bacon et al., 1995). In concert with other T_H1 cytokines, IL-12 was shown to exert immunostimulatory effects on various cell populations comprising cell-mediated immunity (CMI), including NK cells, dendritic cells (DCs), neutrophils, NKT cells, and cytotoxic T lymphocytes (CTLs) (Collison et al., 1998; Cui et al., 1997; Grohmann et al., 1998; Mehrotra et al., 1993; Robertson et al., 1992). Anti-tumor effects of IL-12 have been reported in various animal models, and have been well established (Colombo and Trinchieri, 2002). For example, intratumoral administration of IL-12 in mice was shown to promote systemic anti-tumor immunity and potentiate host ability to eradicate micrometastases (Rosenberg et al., 1998). Our previous work has utilized IL-12 peri-operatively, and this intervention increased resistance to experimental metastases, which we and others have shown to be promoted by surgery and other immunosuppressive stress paradigms (Schwartz et al., 2008).

However, despite the promising findings from many animal studies regarding the beneficial effects of IL-12 in the context of cancer immunotherapy and surgery, it appears that the use of IL-12 in the clinical setting has yielded rather limited results (Atkins et al., 1997; Colombo and Trinchieri, 2002; Hurteau et al., 2001; Portielje et al., 1999), similar to other therapeutic approaches tested in animal models. Several difficulties in simulating the development of human cancer by animal models were suggested

* Corresponding author. Fax: +972 3 640 9520.
E-mail address: shamgar@post.tau.ac.il (S. Ben-Eliyahu).

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