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Review

The Y_1 receptor for NPY: A key modulator of the adaptive immune system

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ABSTRACT

Growing evidence suggests that the neuropeptide Y (NPY) system plays an important role in the immune system. Yet, little is known about the expression of NPY and receptors in the immune system. Moreover, original contradicting results have confused the picture and hampered a clear understanding of its role in the immune system. The use of Y_1 receptor-deficient mice, combined with advanced methods to investigate immune functions, have provided the solution to the problem raised by previous disparities. From results obtained using Y_1-deficient mice ($Y_1^{-/-}$), we uncovered a bimodal role for Y_1 on immune cells. Y_1 expression on antigen-presenting cells (APC) is essential for their function as T cell priming elements. Conversely, Y_1 signaling in T cells plays a regulatory role without which T cells are hyper-responsive. The opposite role of Y_1 on APC and T cells has reconciled previous disparities by showing that signaling via Y_1 protects against inflammation by inhibiting T cell responses, whereas $Y_1^{-/-}$ mice are protected in the same inflammatory models due to defective APCs.

Contents

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Abbreviations: NPY, neuropeptide Y; APC, antigen-presenting cell; DC, dendritic cell; Th, T helper; MS, multiple sclerosis; EAE, experimental autoimmune encephalomyelitis; DSS, dextran sodium salt; DTH, delayed type hypersensitivity; MLR, mixed lymphocyte reaction; TLR, Toll-like receptor

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1. Introduction

The induction of an adaptive immune response is a complex process involving the coordination of a number cell types and molecules. Antigen-presenting cells (APCs) trap, process and present antigens to naïve T lymphocytes which then differentiate into antigen-specific effector cells. More specifically, macrophages and dendritic cells (DCs) act as APCs, taking up antigen and presenting it to $CD8^+$ and $CD4^+$ T cells as peptide fragments bound to MHC class I or class II molecules, respectively. The interaction between T cells and APCs is a fundamental step in the induction of an adaptive immune response, which sets the stage for the proper activation of both T and B cell antigen-specific effector functions. Newly activated T cells can differentiate into T helper (Th) 1 or 2 cells, depending on the cytokine environment. Appropriate activation of APCs is a pivotal event in determining the polarization of T cell responses, and, for instance, production of IL-12 by APCs, is key to promote Th1 T cell differentiation. IL-12 acts directly on T cells to induce proliferation and IFNγ production and in combination with IFNγ to promote isotype switching to IgG2a in B cells [9]. Several autoimmune diseases such as multiple sclerosis (MS) and rheumatoid arthritis are caused by a sustained and inappropriate Th1-dominant autoreactive T cell responses.

In recent years the NPY system has emerged as a set of molecules potentially playing an important role in the induction of a number of immune responses by acting on a variety of immune cells. Previously described roles for the NPY system include immune cell distribution, production of cytokine by T helper cells and inflammatory mediator release from macrophages [3]. Further evidence supporting a role for NPY in regulating immune functions comes from the observation that high numbers of NPY containing nerve fibers are present in lymphoid organs, also importantly, interacting with leukocytes [8]. Moreover, the Y_1 receptor for NPY is widely expressed on leukocytes, including T, B cells and APCs such as DCs and macrophages [10].

Two recent studies have described a novel role for NPY via its Y_1 receptor in regulating the induction Th1 responses. In the first study, treatment of mice with NPY or an agonist to the Y_1 receptor suppressed experimental autoimmune encephalomyelitis (EAE), a Th1 T cell-driven autoimmunity model [2]. Conversely, blocking Y_1 receptor signaling using an antagonist to Y_1 resulted in an earlier onset of disease [2]. This data suggested a suppressive role for NPY, via signaling through its Y_1 receptor on T cells. However, a conflicting picture arose from the second study using another Th1-mediated model of inflammatory colitis, the dextran sodium salt (DSS)-induced colitis. In this model, Y_1-deficient mice ($Y_1^{-/-}$) or those treated with a Y_1 receptor antagonist were protected against weight loss and disease activity induced by DSS [5], thus suggesting this time that an absence of Y_1 receptor signaling has a protective effect in this model. The challenge at this stage is to explain why Y_1 signaling protected in some Th1-mediated settings and yet participated in inflammation in some others.

2. Immunological phenotype of $Y_1^{-/-}$ mice and new clues

To further dissect the role of the Y_1 receptor in regulating immune responses, we examined the immunological phenotype of $Y_1^{-/-}$ mice [10]. Mice lacking the Y_1 receptor had smaller spleens than WT controls, and this correlated with a global reduction in B cell numbers in all secondary lymphoid organs [10]. Reduced B cell numbers had little effect on total serum Ig levels; however, a specific loss of IgG2a production was observed, and this was not corrected upon antigen challenge [10]. In addition, initial evidence for an impairment of T cell activation in $Y_1^{-/-}$ mice arose from the reduced ratio of effector to naïve T cells observed in the lymph nodes of these mice, despite normal T cell development in the thymus [10]. Using a

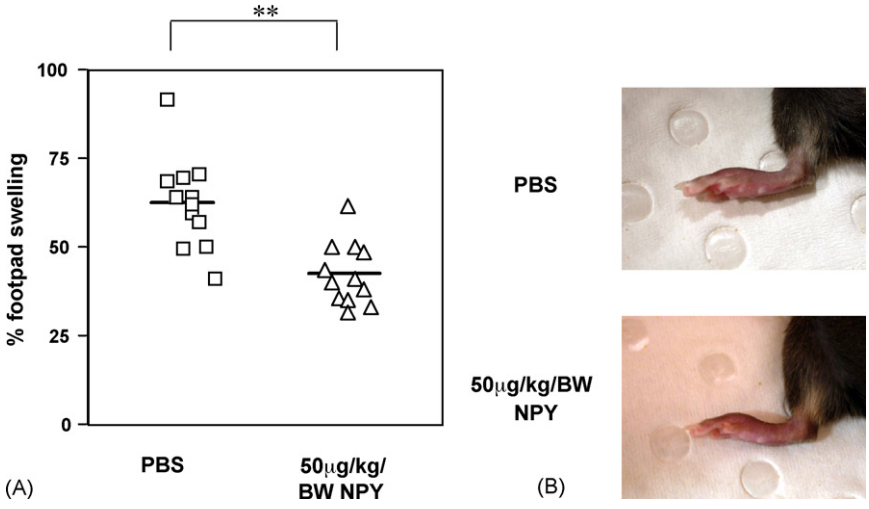

Fig. 1 – NPY inhibits footpad swelling elicited in a DTH response. (A) Footpad swelling in WT mice 24 h after secondary challenge with mBSA (n = 10–12 mice per group). Mean values represented by black bars. Each symbol represents an individual animal. Squares: i.p. PBS injection daily. Diamonds: 50 μg/ml NPY injected daily i.p. $^{**}P < 0.005$ as determined by t-test. Footpad swelling was measured using a caliper and calculated as described previously [4]. (B) Pictures of an inflamed paw of a mouse injected with PBS (top panel) or NPY (bottom panel) i.p. daily, representative of (A).