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Norman Cousins Lecture

The beta2-adrenergic receptor on T and B lymphocytes: Do we understand it yet?

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ABSTRACT

The role played by the beta2-adrenergic receptor (β_2AR) in regulating the level of T and B lymphocyte function has been studied for over half a century. During this time, we have learned that T and B lymphocytes express almost exclusively the β_2AR, and that the level of expression on a specific lymphocyte subset differs due to epigenetic regulation by histone and DNA methylation. We have also learned that engagement of the β_2AR on lymphocytes, by either norepinephrine or a selective pharmacologic ligand, regulates the level of lymphocyte activity differentially, depending on the time of receptor engagement in relation to the activation and differentiation state of the cell, the molecular signaling pathway activated, and the cytokine microenvironment. The challenge now is to determine if we understand enough about how this receptor functions on lymphocytes to predict the relevance of such regulation to overall immune homeostasis and the development/progression of human disease.

1. Introduction

It was Norman Cousins who challenged all of us to determine the mechanism by which he survived two major illnesses, ankylosing spondylitis, and a near-fatal heart attack, simply by harnessing the power of human emotions. When he was taken to the hospital for the heart attack, he said, "...I want you to know that you're looking at the darnedest healing machine that's ever been wheeled into this hospital". He believed that the mind and body were connected somehow and that each could help the other to heal. Exactly how this communication occurred to bring about healing was a mystery to him, but he knew it was real and that an understanding of the mechanism would lead to cures that were unimaginable. For the past 50 years, a number of researchers have accepted this challenge to study this connection between the mind and body, in particular, to determine the mechanism responsible for mediating the effect on health.

A fine balance exists in the body to maintain health and overall homeostasis. This balance is maintained by the proper functioning of every organ system. One participant in this balance equation involves the immune system, which evolved to protect us not only from the environment around us, which is filled with infection-causing microorganisms, allergens, and cancer-promoting agents, but also from the environment within us, which can develop transformed cells that cause cancer and autoimmune disease (Fig. 1). It is essential that a mechanism exists to coordinate these organ systems to respond immediately to a threat and to bring the organ systems back to normal after the crisis subsides. One key mechanism responsible for such coordination involves the autonomic nervous system, which serves as the messenger from the mind to the body for all organ systems, including the immune system (Fig. 2; Ader et al., 1990; Nance and Sanders, 2007). Another key mechanism responsible for such coordination involves cytokines, which serve as the messenger to the brain from the activated immune cells that are responding to an external or internal threat (Besedovsky et al., 1983). These two mechanisms of communication between the brain and immune system are now known to play a major role in maintaining a protective balance in the body to maintain health and homeostasis.

2. Expression of the β_2AR on T and B lymphocytes

The autonomic nervous system is composed of two distinct systems, namely the sympathetic and parasympathetic nervous systems that secrete norepinephrine and acetylcholine,

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Fig. 1. Immune system protection is a balancing act. The immune system keeps our health in balance by protecting us against not only external threats such as infectious microorganisms that cause disease, allergens that precipitate allergy and asthma, and environmental agents that cause disease/cancer, but also internal threats such as self-antigens that cause autoimmune disease and transformed cells that cause cancer.

respectively. The parenchyma of lymphoid organs are innervated primarily by sympathetic nerve fibers that release norepinephrine within hours of antigen recognition by immune cells (Felten et al., 1985). The released norepinephrine binds to either alpha- or beta-adrenergic receptors that are expressed by immune cells, although T and B lymphocytes express the beta2-adrenergic receptor (β_2AR) almost exclusively (Sanders et al., 2001). Engagement of the β_2AR activates a cascade of signaling intermediates, including cAMP and protein kinase A, which leads to the phosphorylation of cellular proteins, including transcription factors that mediate gene expression. For the purposes of this review, only B cells and CD4+ T cells will be discussed. Murine B cells express the β_2AR, as do naïve CD4+ T cells and effector Th1 cells, while effector Th2 cells do not (Fig. 3; Sanders et al., 1997). Differential expression in human effector CD4+ T cells remains unclear, mainly due to the difficulty in generating and isolating a homogenous population of cells that secrete just one cytokine profile. Nonetheless, the differential expression found in murine cells is due to epigenetic factors involving histone modifications and DNA methylation. Epigenetic mechanisms do not cause any change in the DNA itself, but involve postsynthetic modifications to DNA and/or DNA-associated histones that remodel chromatin, are heritable, and occur during and after early development. Th1 cells that develop from a naïve CD4+ T cell increase the level of β_2AR expression as compared to naïve cells via a mechanism that involves histone-3 and -4 acetylation and histone-3 lysine-4 methylation (McAlees and Sanders, 2009). In contrast, Th2 cells that develop from a naïve CD4+ T cell dramatically repress the level of β_2AR expression as compared to naïve cells via a mechanism that involves histone-3 and -4 acetylation, histone-3 lysine-4 methylation,

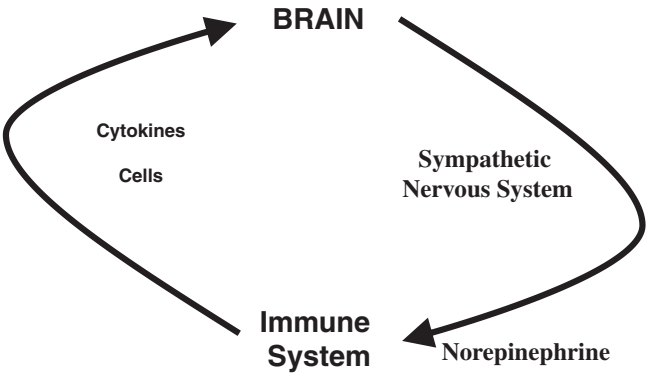

Fig. 2. The brain–immune communication pathway. Activation of the immune system allows for communication with the brain via the release of cytokines from activated immune cells and/or the trafficking of activated immune cells into the brain. Activation of selective regions in the brain allows for communication with the immune system via activation of the sympathetic nervous system centrally and the release of the neurotransmitter norepinephrine from sympathetic nerve terminals that penetrate lymphoid tissue in the periphery.

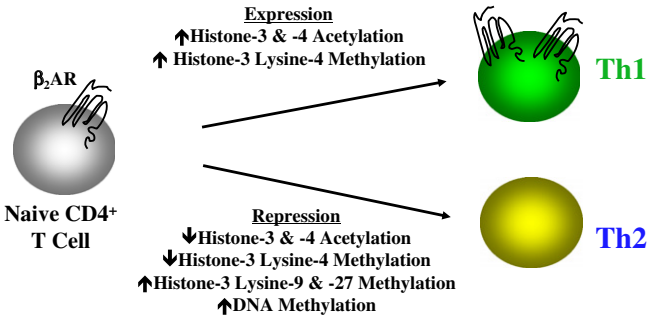

Fig. 3. Epigenetic factors influence beta2-adrenergic receptor expression by murine CD4+ T cell subsets. Naïve CD4+ T cells express the β_2AR protein on the surface and a level of histone acetylation and methylation within the beta2-adrenergic receptor gene promotor. As naïve cells differentiate to a Th1 or Th2 cell that express and repress expression, respectively, the level of histone acetylation and methylation change. The pattern and level of specific histones involved in expression vs. repression is determined by which T cell subset develops. DNA methylation is also involved in beta2-adrenergic receptor repression in Th2 cells.

histone-3 lysine-9 and -27 methylation, and DNA methylation. Thus, an epigenetic mechanism exists to explain the difference in effector T cell expression of the β_2AR, although the clinical relevance for differential expression remains unclear, but will be discussed below.

3. Effect of β_2AR engagement on CD4+ T cell function

The effect of β_2AR engagement on an activated naïve CD4+ T cell vs. an effector Th1 cell was found to be dependent on different factors. β_2AR engagement on an activated naïve T cell cultured in the presence of IL-12 induced more IFN-γ to be produced in comparison to naïve cells activated alone without β_2AR engagement (Fig. 4; Swanson et al., 2001). This increase in IFN-γ was due to a higher level of IFN-γ being secreted per cell by the resulting Th1 cells that developed, as opposed to more Th1 cells being made. As the concentration of IL-12 increased in the presence of β_2AR engagement, so did the amount of IFN-g secreted per Th1 cell that

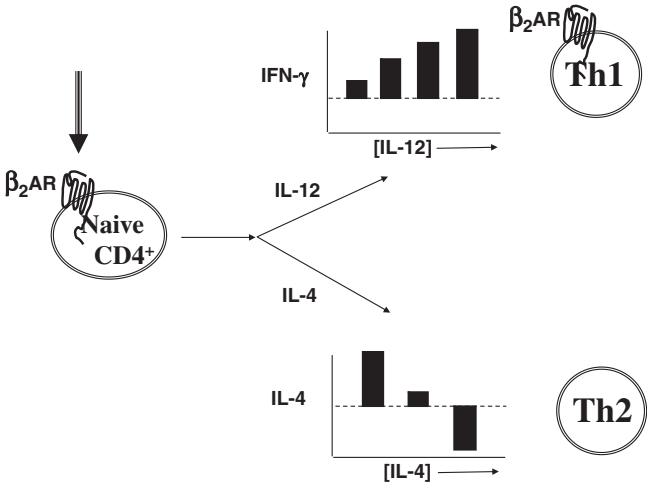

Fig. 4. Beta2-adrenergic receptor engagement on a naïve CD4+ T cells during differentiation influences the level of cytokine produced by the resulting Th1 or Th2 cell. The level of IFN-g produced by the resulting Th1 cells increases in a manner that is not only dependent on the concentration of IL-12 that was available during naïve T cell differentiation, but also depends on an increase in the amount of IFN-g produced per cell as opposed to an increase in the number of Th1 cells that develop. The level of IL-4 produced by the resulting Th2 cells appears to increase when the concentration of IL-4 available during naïve T cell differentiation is low, but decreases as the concentration of IL-4 available during naïve T cell differentiation is elevated.