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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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