Journal of Neuroimmunology 257 (2013) 1–6

Contents lists available at SciVerse ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Review article

Changes of the expressions of immune-related genes after ventromedial hypothalamic lesioning. Systematic review of the literature☆

Takayoshi Kiba *, Kiyomi Yagyu

Division of Modern Medical Technology, Institute for Clinical Research, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Kure, 737-0023, Japan

ARTICLE INFO

Article history:
Received 12 October 2012
Received in revised form 10 January 2013
Accepted 22 January 2013

Keywords:
Immunity
Gene expression
Visceral organs
Hypothalamus

ABSTRACT

Over the past 20 years, the functional autonomy of both the immune and central nervous systems has been successfully challenged. Although the ventromedial hypothalamus (VMH) is one of the centers of parasympathetic nervous system, to date, there has been little reported regarding the role of the hypothalamus in directly changing the expression of immune-related genes. Recently, it has been reported that VMH lesions can directly change the expression of immune-related gene families. The present review focuses on the relationships between the VMH and the expressions of immune-related genes.

Contents

1. Introduction

Over the past 20 years, the functional autonomy of both the immune and central nervous systems (CNS) has been successfully challenged. The neurohumoral activities of the hypothalamus, its anatomical and functional links with cortical and subcortical brain structures, and its regulatory control over many physiological functions made this structure of particular interest for immunological investigations. The CNS can have widespread effects on the immune system following activation of the hypothalamic–pituitary–adrenal axis (Haddad et al., 2002), and the sympathetic nervous system (Madden et al., 1995). The presence of such a close association between sympathetic nerve fibers and cells of the immune system may provide a direct mechanism enabling the CNS to regulate specific aspects of the immune response. It appears that the CNS can communicate with the immune system in a general sense via endocrine outflow from the CNS (i.e., hypothalamically or pituitary controlled hormones such as corticotropin, adrenocorticotropin, and glucocorticoids) to the periphery but also more directly by means of sympathetic innervation of both primary and secondary lymphoid organs (Munck and Guyre, 1991). Consistent with this, the interactions of the nervous system and the immune system have been the subject of a number of critical reviews (Ader et al., 1995). The experimental evidence for nervous system–immune system interactions can be summarized: 1) Alterations in immune responses can be conditioned; 2) electrical stimulation or lesions of specific brain sites can alter immune function; 3) stress alters immune responses and the growth of tumors and infections in experimental animals; and 4) activation of the immune system is correlated with altered neurophysiological, neurochemical, and

Abbreviations: BAFF, B cell-activating factor; CD28, Cluster of Differentiation 28; CISH, cytokine inducible SH2-containing protein; CNS, central nervous system; TCR, T cell receptor; TLR, Toll-like receptors; MH, medial hypothalamus; MHC, major histocompatibility complex; NK, natural killer; VMH, ventromedial hypothalamus.

☆ The authors have stated that there is no conflict of interest from any source for the purpose of writing the manuscript.

* Corresponding author at: Division of Modern Medical Technology, Institute for Clinical Research, National Hospital Organization Kure Medical Center Chugoku Cancer Center, 3-1, Aoyama-cho, Kure-shi, Hiroshima, 737-0023, Japan. Tel.: +81 823 22 3111; fax: +81 823 21 0478.
E-mail address: kibat@kure-nh.go.jp (T. Kiba).

0165-5728/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jneuroim.2013.01.010

Table 1
Upregulated (>2-Fold) and downregulated (>2-Fold) immune-related genes identified by DNA microarray analysis at 3 days in liver, pancreas, and intestine after VMH lesioning.

Gene name	Functions	Reported phenotypes in knockout mice	Reported organ specific phenotypes in knockout mice
1) Upregulated genes			
➢ T cell function			
- Liver			
Tumor necrosis factor receptor superfamily (TNFRSF9)	Contributing to the clonal expansion, survival, and development of T cells, inducing interferon-γ expression proliferation in peripheral monocytes, enhancing T cell apoptosis induced by TCR/CD3 triggered activation, and regulating CD28 co-stimulation to promote Th1 cell responses.	Having normal T and B cell numbers but having defects in antigen-specific and cytolytic T lymphocyte activity (Kwon et al., 2002). Not generating a rapid IL-4 response after systemic T cell activation, or effective Ag-specific Th2 responses, and reducing natural killer -specific cytolytic activities (Vinay et al., 2004).	Decreasing CD8 T cell accumulation in the lungs (Lin et al., 2009). Enhancing ovalbumin-specific Th1 and Th2 responses in the spleen (Lee et al., 2005).
- Intestine			
Transcription factor 3 (E2A immunoglobulin enhancer binding factors E12/E47) (TCF3)	Playing major roles in determining tissue-specific cell fate during embryogenesis, like muscle or early B-cell differentiation.	Developing thymic lymphoma, generally within 2.5–8 months of age (Engel and Murre, 2002).	Unreported.
Interleukin 1 receptor -like 1 (IL1RL1)	Being induced by proinflammatory stimuli, and being involved in the function of helper T cells.	Exhibiting an increased susceptibility to polymicrobial infection with impaired bacterial clearance (Buckley et al., 2011).	Unreported
➢ NK cell function			
- Pancreas			
Major histocompatibility complex, class I, G (HLA-G)	Being involved in the presentation of foreign antigens to the immune system, and playing a role in maternal tolerance of the fetus by mediating protection from the deleterious effects of natural killer cells, cytotoxic T lymphocytes, macrophages and mononuclear cells	Unreported	Unreported
2) Downregulated genes			
➢ B cell function			
- Liver			
Tumor necrosis factor receptor superfamily 13 (TNFRSF13C)	Encoding a receptor for B cell-activating factor (BAFF), being a type III transmembrane protein containing a single extracellular cysteine-rich domain, and being the principal receptor required for BAFF -mediated mature B-cell survival.	Depleting B2 cells but not B1a cells selectively (Kyaw et al., 2012). Displaing strongly reduced late transitional and follicular B cell numbers and being essentially devoid of marginal zone B cells (Sasaki et al., 2004).	Unreported
➢ T cell function			
- Intestine			
Cytohesin 1 (CYTH1)	Expressing in natural killer and peripheral T cells, and regulating the adhesiveness of integrins at the plasma membrane of lymphocytes.	Unreported	Unreported
Inducible T-cell co-stimulator (ICOS)	Enhancing all basic T-cell responses to a foreign antigen, and effective helping for antibody secretion by B-cells.	Showing greatly enhanced susceptibility to experimental autoimmune encephalomyelitis (Dong et al., 2001).	Reducing natural killer T cell population in the liver and spleen (Watanabe et al., 2010).
➢ NK cell function			
- Intestine			
Cytohesin 1 (CYTH1)	Expressing in natural killer and peripheral T cells, and regulating the adhesiveness of integrins at the plasma membrane of lymphocytes.	Unreported	Unreported
CD244 molecule, natural killer cell receptor 2B4 (CD244)	Encoding a cell surface receptor expressed on natural killer cells (and some T cells) that mediate non-major histocompatibility complex restricted killing.	Developing activated CD4 T cells and B cells, increased numbers of T follicular helper cells, and a proportion develop autoantibodies to nuclear antigens (Brown et al., 2011). Establishing an inhibitory function for this receptor on natural killer cells both in vitro and in vivo (Waggoner et al., 2010).	Unreported
➢ Cytokine function			
- Liver			
Cytokine inducible SH2 -containing protein (CISH)	Containing a SH2 domain and a SOCS box Domain, belonging to the cytokine-induced STAT inhibitor, and being also known as suppressor of cytokine signaling or STAT-induced STAT inhibitor, protein family.	Unreported	Unreported