



Immunoresolvents signaling molecules at intersection between the brain and immune system

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Understanding mechanisms that control immunity is central in the quest to gain insights into the etiopathology of many of the diseases that afflict modern societies. New results implicate the nervous system as a central player in controlling many aspects of both the innate and adaptive arms of the immune response. Furthermore it is now well appreciated that a novel group of autacoids termed as specialized proresolving mediators, which are enzymatically produced from essential fatty acids, orchestrate the immune response promoting the termination of inflammation as well as tissue repair and regeneration. The present brief review discusses evidence for the crosstalk between the nervous system and leukocytes in regulating SPM production. We will also discuss the impact that this has on controlling tissue resolution tone and the resolution of both infectious and sterile inflammation.

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Current Opinion in Immunology 2018, 50:48–54

This review comes from a themed issue on Innate immunity

Edited by Gwendalyn Randolph

<https://doi.org/10.1016/j.coi.2017.10.007>

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Introduction

The nervous system integrates signals from the periphery to ensure homeostatic control and host survival. Increasing evidence demonstrates that in addition to regulating sensory and motor functions the nervous system is also essential in regulating the host immune response [1]. This crosstalk between the immune and nervous systems is a primordial defense mechanism where, for example, in the nematode *Caenorhabditis elegans* the nervous system is central in controlling innate immunity via the modulation of the non-canonical unfolded protein response [2]. In mammals the nervous system is also important in

controlling both the innate and adaptive arms of the immune responses [1,3,4]. Recent studies demonstrate that the vagus nerve orchestrates host responses to both sterile, including sterile peritonitis [5], arthritis [6], colitis [7] and cancer [4] as well as infectious insults, for example, polymicrobial sepsis [8] and *Escherichia coli* infections [3]. These observations have been extended to humans where in patients with arthritis stimulation of the vagus system leads to a significant reduction in disease activity and in circulating markers of inflammation [9].

Efforts to identify signals that control the termination of inflammation recently uncovered a genus of mediators that are produced via the stereoselective conversion of essential fatty acids. These autacoids activate cognate receptors and regulate the biological actions of both innate and adaptive immune cells [10]. Given their potent actions and unique structures these mediators are coined as specialized pro-resolving mediators (SPM). This super-family of mediators is composed of four main families: the arachidonic acid derived lipoxins, the eicosapentaenoic acid (EPA), *n*–3 docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA)-derived resolvins (Rv) and the *n*–3 DPA and DHA-derived protectins (PD) and marins (MaR) (see [11,12] for a detailed review of their biosynthetic pathways). The production of these mediators is regulated in both a temporal and tissue dependent manner. Recent studies demonstrate that the biological actions of RvD1 (see Table 1 for complete stereochemistry), a DHA-derived SPM, are additive to those of antibiotics reducing the required doses to clear both gram positive and negative infections [13]. These mediators also regulate tissue repair and regeneration by controlling leukocyte trafficking, phenotype, the expression of genes that are involved in the regeneration of damaged tissues and the re-establishment of barrier function [14–16]. Impaired LXA₄ production is associated with dysregulated T-cell response in dry eye disease [17]. RvD1, RvD2 and MaR1 also regulate T-cell phenotype, down-regulating the production of effector cytokines, including IFN γ , in both CD4 and CD8 positive T-cells. They also promote the expression of FoxP3 in CD4 cells [18]. The RvD series precursor 17-HDHA regulates B-cell responses to viral infections, up-regulating antibody production and protecting against influenza infections [19] and pain [20,21]. The EPA derived RvE1 regulates the responses of antigen presenting cells, including those of dendritic cells reducing the expression of IL-12 [22,23]. Together these findings emphasize the role of this new super-family of

Table 1**Lipid mediator metabolomes, abbreviations and complete stereochemistry.**

Metabolome	Mediator	Abbreviation	Stereochemistry
DHA	Resolvin D1	RvD1	7S, 8R, 17S-trihydroxy-4Z, 9E, 11E, 13Z, 15E, 19Z-docosahexaenoic acid
	Resolvin D2	RvD2	7S, 16R, 17S-trihydroxy-4Z, 8E, 10Z, 12E, 14E, 19Z-docosahexaenoic acid
	Resolvin D3	RvD3	4S, 11R, 17S-trihydroxy-5Z, 7E, 9E, 13Z, 15E, 19Z-docosahexanoic acid
	Resolvin D4	RvD4	4S, 5R, 17S-trihydroxy-6E, 8E, 10Z, 13Z, 15E, 19Z-docosahexaenoic acid
	Resolvin D5	RvD5	7S, 17S-dihydroxy-4Z, 8E, 10Z, 13Z, 15E, 19Z-docosahexaenoic acid
	Maresin 1	MaR1	7R, 14S-dihydroxy-4Z, 8E, 10E, 12Z, 16Z, 19Z-docosahexaenoic acid
	Protectin conjugate in tissue regeneration 1	PCTR1	16R-glutathionyl, 17S-hydroxy-4Z, 7Z, 10Z, 12E, 14E, 19Z-docosahexaenoic acid
	Protectin conjugate in tissue regeneration 2	PCTR2	16-cysteinylglycyl, 17S-hydroxy-4Z, 7Z, 10Z, 12, 14, 19Z-docosahexaenoic acid
	Protectin conjugate in tissue regeneration 3	PCTR3	16-cysteinyl, 17S-hydroxy-4Z, 7Z, 10Z, 12, 14, 19Z-docosahexaenoic acid
EPA	Resolvin E1	RvE1	5S, 12R, 18R-trihydroxy-6Z, 8E, 10E, 14Z, 16E-eicosapentaenoic acid
AA	Lipoxin A ₄	LXA ₄	5S, 6R, 15S-trihydroxy-7E, 9E, 11Z, 13E-eicosatetraenoic acid
	Leukotriene B ₄	LTB ₄	5S, 12R-dihydroxy-6Z, 8E, 10E, 14Z-eicosatetraenoic acid
	Prostaglandin E ₂	PGE ₂	9-oxo-11R, 15S-dihydroxy-5Z, 13E-prostadienoic acid

autacoids in the maintenance of homeostasis and re-establishment of function following challenge, whether this is sterile or infective in nature.

Several mechanisms are now implicated in the regulation of SPM biosynthesis; regulation of micro RNA 219 controls 5-LOX expression [24]. Post-translation modification of 5-LOX leads to a switch in the product profile of the enzyme from the pro-inflammatory leukotriene (LT) B₄ to the pro-resolving mediator LXA₄ [25]. Sex hormones also play an important role in regulating SPM production, an action that is also tissue dependent, where for example in murine systems estrogen down-regulates LXA₄ production in the eye [17]. In humans this hormone is associated with an increased derman and systemic SPM production including RvD, LX and RvE [26]. Recent results also demonstrate that the nervous system is essential in controlling local SPM formation, during both infectious and sterile inflammation [3,5]. The present review highlights the recent evidence underpinning the role of the nervous system in regulating tissue SPM production and the role of this response in controlling innate immune responses to both sterile and infectious insults.

Neuronal regulation of tissue lipid mediator profiles

Increasing evidence indicates that the initial response by resident leukocytes to both injury and infections has a significant bearing on outcome of the ensuing inflammation and whether this resolves or becomes chronic [27].

Given the roles that the vagus nerve plays in regulating host immune responses [1,8,9], we recently queried whether this nerve was also involved in the tempering of tissue leukocyte phenotype and responses. Using a systematic approach we found that cervical disruption of the vagus nerve lead to a shift in peritoneal concentrations of both pro-resolving as well as inflammation initiating eicosanoids [3]. Peritoneal prostaglandin concentrations were increased in vagotomised mice whereas concentrations of several pro-resolving mediators including the recently uncovered immunoresolvents Protectin Conjugates in Tissue Regeneration (PCTR) were decreased. Of note, cervical disruption of the left vagus did not significantly perturb peritoneal PCTR levels suggesting that the neuro-immune plexus was in this organ was associated with the right vagus. These changes in peritoneal lipid mediator concentrations point to a significant alteration in the ability of the host to mount a protective immune response given the increase in inflammation-initiating eicosanoids and a decrease in the tissue protective mediators; a lipid mediator profile associated with delayed/non-resolving inflammation [10,28,29].

Vagus regulates PCTR biosynthesis in peritoneal ILC-3 and macrophages

Changes in peritoneal levels of these mediators were also associated with an alteration peritoneal leukocyte composition, phenotype and functions. Loss of vagal signaling impacted group 3 innate lymphoid cells (ILC-3). The observation that ILC-3 numbers were significantly

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