



Thematic Minireview Series: Inflammatory transcription confronts homeostatic disruptions

Published, Papers in Press, June 14, 2017, DOI 10.1074/jbc.R117.801753

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Edited by Chris Whitfield

In this Thematic Minireview Series, three stimulating articles are presented: one on long non-coding RNAs, another on the ligand-activated transcription factor aryl hydrocarbon receptor, and the third on how docosanoids modulate transcriptionally modulated homeostasis and ultimately cell survival in the retina and brain.

Relationships are key, both in life and in the life of a cell. This is particularly important when cells need to confront potential disruptors of homeostasis to prevent chaos and disease onset. The homeostasis concept was developed by Harvard physiologist Walter Bradford Cannon in 1932 (1). Today we bring homeostasis to the molecular level when considering how the inflammatory response triggers transcriptional regulation to sustain cellular integrity. The response is initially a defensive reaction that includes immune cells, blood vessels, neurons, astrocytes, macrophages, microglia, retinal pigment epithelial cells, and other cells to sustain homeostasis by removing the triggering factor(s) and cell debris and then to set in motion cellular and tissue restoration. Some of the responses overcome the homeostasis disruptor, leading to resolution, whereas others would be unable to restore balance, setting up the onset and progression of diseases often reflected in disrupted homeostasis and the triggering of a complex, failed inflammatory response. In many tumors, inflammation orchestrates a microenvironment beneficial to proliferation, cancer cell survival, and migration. The principles governing these crucial responses are beginning to be unraveled at the transcription level. Furthermore, there is an intimate relationship between the immune system and the inflammatory response at the transcriptional level that is allowing for integrated responses and deciphering of the molecular principles engaged. In fact, to make this happen, there must be a convergence of genetic and environmental factors (pollutants), as well as diet and the microbiome.

This work was supported by National Institutes of Health Grants GM103340, EY005121, and NS046741 (to N. G. B.). The authors declare that they have no conflicts of interest with the contents of this article. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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lncRNAs and their transcriptional control of inflammatory responses

Mathy and Chen (2) refer to the evolving role of long non-coding RNAs (lncRNAs)² as transcriptional regulators of the inflammatory response. A group of lncRNAs is induced as part of the response to inflammation and acts as an enhancer or a suppressor of inflammatory transcription, with members behaving as scaffolds with RNA-binding proteins in chromatin-remodeling complexes. lncRNAs augment the inflammatory response by enhancing the transcription of pro-inflammatory target genes or inflammatory signals. On the other hand, lncRNAs suppress or limit the magnitude of the inflammatory response by limiting the transcription of pro-inflammatory cytokines, or of the availability of inflammatory signal pathways. The review also discusses specific examples such as lincRNA-EP3, which down-regulates expression of immune response genes in macrophages. Upon microbial activation, this suppression is released, and gene transcription is activated. Also lincRNA-Cox-2 performs both as an enhancer and as a suppressor of inflammation in a gene-specific manner. These refined modulatory events are engaged in a facilitating induction of specific sets of lncRNAs during inflammation that, in turn, provide modulatory feedback to the inflammatory responses. Therefore, the authors propose targets for novel therapeutic strategies involving lincRNAs for diseases that involve failed inflammatory outcomes.

Control of immune-mediated pathology via the aryl hydrocarbon receptor

Wheeler, Rothhammer, and Quintana (3) focus on the significance of the aryl hydrocarbon receptor, a ligand-activated transcription factor, in molding the immune response when exposed to multiple cues from the diet, environmental pollutants, and the gastrointestinal microbiome. Among the key cells in these processes are astrocytes, which play a definitive role in nervous system development, synapse functioning, interactions with microglia during multiple sclerosis pathogenesis, recruitment of monocytes, neuronal plasticity, and circuitry repair. Astrocytes release neurotoxic pro-inflammatory mediators such as TNF- α , reactive oxygen species, IL-6 and IL-1 β ,

² The abbreviations used are: lncRNA, long non-coding RNA; lincRNA, long intergenic non-coding RNA; AhR, aryl hydrocarbon receptor; DHA, docosahexaenoic acid.

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and nitric oxide. On the other hand, these cells are also able to release anti-inflammatory mediators, including IGF-1 and ciliary neurotrophic factor (CNTF). This review also discusses how type-I interferons (IFN-Is) activate AhR expression in astrocytes, consequently leading to AhR-dependent inflammatory modulatory transcriptional responses. AhR activity is regulated by molecules formed from dietary tryptophan by commensal bacteria, pointing to an important connection with the gut–brain signaling axis as a controller in the development of inflammatory and neurodegenerative pathology. The review discusses the consequences of these events, namely modulation of neuroinflammation in the central nervous system, and the potential therapeutic applications to autoimmune diseases, such as multiple sclerosis.

Molecular mechanisms of signaling via the docosanoid neuroprotectin D1 for cellular homeostasis and neuroprotection

Asatryan and Bazan (4) highlight emerging questions of the regulation of inflammatory transcription when photoreceptors and retinal pigment epithelium are confronted with homeostatic adversities. The answers to these questions are needed to better our understanding of, and to develop therapies for, retinitis pigmentosa, macular degenerations, and other retinal diseases. A key novel regulator of inflammatory transcription in the retinal pigment epithelium cell is neuroprotectin D1 (NPD1). This lipid mediator belongs to the docosanoid family, biologically active derivatives of docosahexaenoic acid (DHA). This connection between the regulation of inflammation with DHA derivatives is of interest because this fatty acid belongs to

the omega-3 essential fatty acid family, which is selectively enriched and avidly retained in the nervous system during synaptogenesis and photoreceptor biogenesis. The potent and stereoselective mediator NPD1 is the first discovered bioactive DHA-derived mediator derived. NPD1 synthesis is up-regulated as an early response to oxidative stress and to neurotrophins in a cell polarity-dependent fashion. NPD1 selectively modulates c-Rel and BIRC3 transcription to control inflammatory responses both in the retina and in the brain. Therefore, the NPD1 responds to homeostatic challenges, and thus regulates photoreceptor cell integrity (for vision) and neuronal cell survival to restore, preserve, and protect synapse formation, circuitry remodeling, and plasticity (for cognition). Further elucidation of mechanisms of action of NPD1 and other docosanoids will contribute to managing diseases, including stroke, Alzheimer's disease, age-related macular degeneration, traumatic brain injury, Parkinson's disease, and other neurodegenerative diseases.

References

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