Resolution of Inflammatory Responses: a brief introduction

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Abstract

Resolution of inflammatory responses is the regulatory process that prevents prolonged inflammation, thus avoiding diseases such as atherosclerosis, rheumatoid arthritis and transplant rejection. There are various different aspects to this process which are discussed briefly here and in the accompanying papers from this Focused Meeting.

The resolution of inflammatory responses is a tightly co-ordinated active process that limits inflammation to the acute phase. It prevents prolonged inflammation, which can damage tissues and trigger diseases such as atherosclerosis, rheumatoid arthritis and rejection of transplanted organs. The resolution phase is regulated at the molecular level by multiple negative-feedback mechanisms that suppress pro-inflammatory signalling and also through apoptosis and clearance of inflammatory cells. This edition of *Biochemical Society Transactions* will highlight how modulation of key signalling pathways in the inflammatory process can lead to attenuation of the inflammatory response. The ability of physiological interventions, such as oxidative stress, to modify these pathways and thereby block resolution will also be explored.

The NF-κB (nuclear factor κB) family of transcription factors triggers inflammatory responses through induction of cytokines, chemokines, acute-phase proteins, adhesion proteins and other inflammatory molecules [1]. NF-κB dimers (e.g. p65–p50) are sequestered in the cytoplasm of unstimulated cells through binding to inhibitory IκB (inhibitor of NF-κB) molecules, which mask their nuclear localization sequences [2]. Signalling through the TNFR1 (tumour necrosis factor α receptor), IL-1R (interleukin-1 receptor), TLRs (Toll-like receptors) and other pro-inflammatory receptors proceeds through distinct signalling intermediaries and leads to the activation of IKKs (IκB kinases), which are responsible for phosphorylation of IκB proteins. The phosphorylated form of IκB is then ubiquitinated and transported to the proteasome where it is degraded, thus liberating NF-κB for nuclear entry [2]. NF-κB activation is regulated by multiple negative-feedback mechanisms, including NF-κB-dependent induction of IκB.

On pp. 263–266, Professor Michael White (Liverpool, U.K.) [3] discusses negative-feedback loops in NF-κB signalling in more detail and describes how they regulate NF-κB oscillation between the cytoplasm and the nucleus. Professor Dr Michael Naumann (Otto-von-Guericke-University, Germany) [4] discusses the control of IκBα in pathogen infections on pp. 267–269. In addition, Dr Toby Lawrence (Imperial College London, U.K.) [5] presents evidence on pp. 270–272 to show that a second ‘alternative’ NF-κB pathway (IKKα) functions to limit acute inflammation and promote the development of adaptive immunity. Although the serine antiprotease SLPI (secretory leucocyte protease inhibitor) was traditionally thought to act extracellularly to...
Protect lung tissue from excessive protease activity, Dr Cliff Taggart (Dublin, Ireland) [6] illustrates on pp. 273–276 that SLPI can also enter cells, become localized to the nucleus and bind to NF-κB-binding sites thus inhibiting binding of p65 NF-κB subunits and subsequent activation of pro-inflammatory genes. In addition, on pp. 277–280, Professor Jacque Piette (Liege, Belgium) [7] discusses how SHIP1 (Src homology 2-containing inositol phosphatase-1) phosphatase regulates the viability and proliferation of lymphocytes, in part by modulating NF-κB.

It has become clear that PTMs (post-translational modifications) in addition to classic phosphorylation can markedly affect the activity of signalling molecules. On pp. 281–283, Dr Kazuhiro Ito (Imperial College London, U.K.) [8] discusses the effect of acetylation, and other PTMs, on the crosstalk between RelA and the glucocorticoid receptor. The idea of a ‘protein code’ analogous to the ‘histone code’ will also be discussed in his paper.

Macrophages are critical to the removal of apoptotic cells [9] and Dr Paul Kirkham (Novartis, U.K.) [10] highlights on pp. 284–287 a mechanism through which oxidative stress alters the extracellular matrix environment of macrophages via the production of reactive carbonyls, thereby altering their adhesion, activation and phagocytic properties. In particular, he will discuss the hypothesis that increased inflammatory mediator release may result from the effect of carbonyl stress on nuclear co-repressor proteins such as HDAC (histone deacetylase). 2. Granulocyte apoptosis is essential for resolution of an acute inflammatory response. On pp. 288–291, Professor Adriano Rossi (Edinburgh, U.K.) [11] discusses this process and provides evidence that activation of a novel mechanism of granulocyte apoptosis at the peak of granulocyte recruitment can dramatically enhance the resolution phase of inflammation.

Collectively, these papers represent a snapshot of the multiple molecular and cellular processes that co-ordinate the resolution of inflammatory processes.

References

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