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Introduction

The resolution of inflammation: New mechanisms in patho-physiology open opportunities for pharmacology

The physiological nature of inflammation is often forgotten as we read and hear about diseases that burden Western societies, with more and more pathologies being identified to present – at least in part – an inflammatory component in their pathogenesis. Classical inflammatory diseases include arthritides and vasculatides together with the rarer auto-inflammatory syndromes; these pathologies are now joined by diseases classically grouped under the cardiovascular or central nervous system domains. As it happens, our body sets in motion the processes that we define as inflammation when there is a disturbance on the natural homeostasis: our reaction to this disturbance manifests with cardinal macroscopic signs as taught to undergraduate students, and we all recognise when we experience inflammation, such as redness, swelling, fever and pain.

The disturbance that provokes initiation of the inflammatory response may be of internal or external nature. The latter is easier to explain and is exemplified by intrusion of viruses, bacteria or xenobiotic products (e.g. bee or snake venoms). The internal disturbance has been appreciated more recently and explained in a ground breaking way by Medzhitov, whereby local events within a given organ are regularly monitored by sentinel cells, distributed within the tissue parenchyma: macrophages and mast cells can sense alteration from the balance and activate subliminal localised responses [1]. When the intensity or the duration of the inflammatory insult that incite the off-balance status are too high, then an organised response takes place and this involves the arrival of helpers and soldiers, such as immune cells. Immune cell recruitment to the site of inflammation requires contribution from other tissutal cells like endothelial cells, pericytes, keratinocytes, fibroblasts, epithelial cells, podocytes and so forth – depending on the affected organ. Internal disturbances are being appreciated as anomalies or phenotypic changes within the tissue cells perhaps of genetic nature or, as more recently discovered, metabolic alterations [2,3]. Thus, endocrine and metabolic diseases like diabetes and obesity fall within the ever-increasing group of inflammatory pathologies. All this without even considering cancer, where the nature of the inflammatory response is subverted and exploited by the proliferating tumoral cells [4–6].

Notwithstanding this brief overview, as said above we now fully appreciate that the host inflammatory response is programmed to terminate ensuring that the affected organ goes back to its pre-inflammatory settings back to performing its normal function. Therefore the most frequent problem is not how or if inflammation starts but why it fails to resolve. This Focused Issue of Seminars of Immunology is set out to address and elaborate a simple question: how does inflammation terminates?

The common view on chronic inflammation, seen as the off-the-balance mechanisms that are operative in the different groups of diseases briefly mentioned above, is that it results from over-exuberant, over-shooting and exaggerated pro-inflammatory signals and processes that drive pathology within the given organ/tissue. Aligned with this view is that the eventual resolution occurs by metabolism of pro-inflammatory mediators. However, studies in the last decade and more, have led to the formulation of a new paradigm that indicates how the resolution of inflammation results from the engagement and activation of specific genetic, molecular and cellular programs. This new paradigm abhors the view that processes that dampen inflammation are the same as those that promote resolution. In this issue a selected group of contributors provides a detailed analysis of most recent discoveries within the endogenous resolution arena, aiming to cover its mediators, processes and also elaborate on the opportunities that this step-change in knowledge may imply. A few are discussed below.

1. First 'dogma' of resolution: from start to end

Distinct classes of pro-resolving mediators exist and they are different from those that promote the onset of inflammation. However, there are similarities inasmuch as both pro-inflammatory and pro-resolving mediators can be categorised under the peptide/proteins, bioactive lipids and autacoids groupings. Furthermore, pro-inflammatory mediators set in motion resolution through favouring biosynthesis of pro-resolving mediators or inducing their receptor targets (as an example, TNF-α is the pivotal factor in septic exudates to upregulate expression of a pro-resolving G-protein coupled receptor [7]). It is not surprising that we must now consider the peak of the acute inflammatory response as the beginning of resolution, aligned with a seminal review where the "... beginning programs the end" concept was explained [8]. This new knowledge of resolution strongly corroborates the physiological functions of inflammation that is to stay within limits, both spatial and temporal, and that it is programmed to end!

In this issue, Headland and Norling introduce classes of pro-resolving mediators and receptor targets, explaining how multiple players and mechanisms operate in resolution, presenting novel concepts around the bio-actions of extracellular traps and

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immune-cell derived vesicles. Gilroy and deMayer reason on the central role that macrophages play in resolution and discuss new evidence for novel points-of-contact between the resolution of inflammation and the adaptive immune system, elucidating recent understanding on how this communication takes place. It is plausible that more mechanisms might be operative at this important biological junction, and will be discovered over the next few years, since proper instruction of the adaptive immune response if fundamental for life of the host. Crean and Godson present a very interesting update on the dynamics of inflammation, with a focus on the bioactive lipid mediators that promote inflammation and those that resolve it too. Collectively these three reviews cover multiple aspects of resolution, reasoning on processes and mediators, setting the scene for the other two sections of the focused issue.

2. Second 'dogma' of resolution: inadequacy leads to pathology

Full appreciation of the physiological phase of resolution implies that diseases characterised by persistent inflammation (above we have mentioned a few) can result from the inadequate engagement of resolving pathways (players and targets). Therefore, insufficient activation of pro-resolving processes can allow for the pro-inflammatory response to carry on unabated, leading to possibly irreversible changes within the affected organ/tissue, hence to chronic pathology.

While conceptually linear, this dogma is more difficult to accept since many years of clinical trials and patient analyses have been wasted by the lack of systematic monitoring of effectors of resolution. The reason behind this missed opportunity lies in part to technical requirements; for instance, metabololipidomic analyses are just now emerging in high profile analytical translational studies [9]. In similar part, this lack of knowledge is consequent to ignorance and simply the refuse to appreciate the physiological relevance of resolution. The adoption of unbiased approaches – from genomics to proteomics to indeed lipidomics – is correcting this desolate scenario and identification of alterations in pro-resolving mediators – and therefore processes – are now timidly emerging [10].

Within this themed issue we give relevance to exemplar of high penetrance diseases. Thus, Colgan chiefly covers the impact that this line of research may have in mucosal repair with impact on pathologies of the gut, the lung and liver. A very interesting tissue protective mechanism centred on the extravasated neutrophils is illustrated, probably preluding to more complex biological properties that this cell type may be endowed with in the context of orchestrating resolution. Viola and Soehnlein provide state-of-the art update on how pro-resolving mediators and targets can impact on vascular disease, with atherosclerosis being the culprit, exemplar of a major Western disease with important impact on a variety of cardiovascular episodes. The concept that failed resolution can contribute to athero-pathology is presented and discussed together with the opportunities that this implies for therapeutic intervention. Finally, Buckley and Haworth adapt these concepts to arthritis, of which rheumatoid arthritis is the most common pathology, with an attentive focus on pro-resolving lipid mediators.

3. Third 'dogma' of resolution: pro-resolving based therapeutics

If disease is due, in total or in part, to malfunctioning of resolution, can we use this new knowledge to intervene therapeutically? Since the 19th century, anti-inflammatory drugs have been developed to act by blocking the synthesis of specific pro-inflammatory mediators or antagonising their receptors. In some cases this resulted from serendipity and, for instance, aspirin had been used for nearly hundred years before its ability to inhibit the synthesis of prostaglandin E_2, and other eicosanoids, was demonstrated by Sir John Vane. More recently, great success has been obtained with the development of biologics: antibodies in one form or another that block specific cytokines.

However, it will be of no surprise that based on what discuss above and the statement that by ignoring the physiology of resolution one discards half of the natural processes of inflammation, the same could be said from the therapeutic angle. We propose that innovation for the development of new medicines to treat the so-many inflammatory pathologies can derive from exploiting the tissue protective properties of resolution. By using *only* medicines that block specific pro-inflammatory mediators may not be sufficient, especially if the cause of disease chronicity is linked to inadequate resolution. Therefore, dogma #3 is functionally linked to dogma #2: proper analyses, funding and full commitment can lead to clarify these issues opening new avenues which may lead toward patient-tailored diagnoses and medicines.

Pro-resolving based therapeutics can be obtained in a variety of ways. They could be achieved by developing mimetics to endogenous pro-resolving mediators or agonists at their receptors. Strategies to boost endogenous resolution could also be applied, by elevating the levels of specific endogenous pro-resolving mediators.

Over the years, Charles Serhan has pioneered the area of resolution and this contribution, together with Chiang and Dalli, provides an extensive account of the biology of resolvins, maresins and other omega-3 derived bioactive mediators. Scholarly, the scientific approach of using self-limiting inflammatory exudates as a source of novel pro-resolving mediators is presented. Equally important is the reasoning on where we are with the translational development of this line of research, thus including pharmaceutical approaches and human studies. Innovation in the treatment of chronic disease may not necessarily be obtained with new medicines, but also through a better understanding of current ones, allowing broader use or repositioning. Montero-Melendez presents an excellent review on the therapeutic potential of adrenocorticotropin (ACTH) a hormone with proven clinical efficacy in rheumatoid and gouty arthritis reported in mid '900s. New knowledge in the field of melanocortins can revitalise the use of ACTH and, equally, support the development of novel melanocortin-based drugs. Finally, the scientific creativity required for unveiling the existence and impact of pro-resolving circuits must be adopted to exploit this knowhow for novel drug discovery programmes. Finally, Wallace, Ianaro, Flannigan and Cirino propose us the opportunity that the biology of hydrogen sulphate provides. The transient nature of bioactive gases, even if acting is solution, requires cunning strategies to exploit their beneficial effects. In this review, strategies to harness the bioactions of nitric oxide, carbon monoxide and hydrogen sulphide are discussed. As an example, a viable approach lies in the development of new molecules able to release the gas of interest (e.g. hydrogen sulphide) in vivo.

4. Conclusion

We trust the readership will enjoy reading the series of reviews that form this Issue of Seminars of Immunology focuses on the 'Resolution of Inflammation'. They will find that the studies commented upon, the concepts presented and the implications for inflammation-based diseases elaborated in this thread of reviews are novel and of high impact. Reviews have been selected to illustrate recent discoveries yet to satisfy the aim to cover aspects and