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INTRODUCTION

Resolution of inflammation: from basic concepts to clinical application

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Acute inflammation may protect the body from invading bacteria or viruses and can help to overcome injuries. While such acute inflammatory processes are usually self-limiting and are followed by tissue repair and healing responses, there are some circumstances in which acute inflammation fails to resolve and is subsequently followed by development of chronic inflammation [1, 2]. Chronic inflammatory disorders place a major burden [3, 4] on affected patients and the responsible health care systems. Key inflammatory disorders in this context comprise various diseases such as psoriasis [5], pemphigus vulgaris [6], graft versus host disease [7], allergic asthma [8], rheumatoid arthritis [9], lupus erythematosus [10], neuroinflammatory disorders [11] and multiple sclerosis [12], uveitis [13], Crohn's disease [14], and ulcerative colitis [15]. In addition, atherosclerosis has been identified as a lipid-driven inflammatory disease [16]. Collectively, the above chronic disorders are frequently detected in Western societies [17–27]. They are quite problematic for affected patients, as they may induce tissue alterations and progressive tissue destruction (e.g., bone and cartilage destruction in rheumatoid arthritis) or can induce organ failure (e.g., kidney failure in lupus erythematosus) [19, 28]. Furthermore, chronic inflammation may predispose to cancer. In fact, about 20% of cancer cases in humans are caused by chronic inflammation (e.g., colon cancer in inflammatory bowel diseases) [29, 30]. Moreover, cancer is frequently associated with a chronic inflammatory response in the local microenvironment and such inflammation may profoundly control tumor growth and prognosis [31–33]. These observations underline the unmet clinical need to gain further detailed insights into the pathomechanisms of chronic inflammation and into the signalling pathways that impair resolution of inflammation.

Studies in recent years have unequivocally shown that resolution of inflammation is an actively controlled process rather than a passive procedure in which the pro-inflammatory immune cascade in inflammation simply fizzles out. Resolution of inflammation involves highly coordinated actions of various immune and non-immune cells [1, 34]. Clearance of damaged cells and pro-inflammatory immune cells usually takes place via coordinated processes of cell death such as apoptosis and cell removal such as efferocytosis [35–37]. Additional repair mechanisms may then allow full or at least partial reconstitution of tissue integrity and function. These processes require the tight controlled interaction between various cell types and immune cells such as granulocytes, tissue resident macrophages, innate lymphoid cells, and lymphocytes, and all these cell types have all suggested to play an important role in controlling resolution of inflammation under certain circumstances [37, 38]. Such vital interaction is of utmost importance to foster resolution of inflammation and to achieve tissue homeostasis.

In this special issue of *Seminars in Immunopathology*, several experts in chronic inflammatory and autoimmune diseases have joined forces to discuss current insights into resolution processes in a variety of key inflammatory disorders [5–16]. They will detail the roles of both innate and adaptive immune cells as well as tissue resident cells in regulating the inflammatory processes and in guiding resolution of inflammation. Moreover, they will discuss the role of soluble mediators in tissue inflammation and healing. In this context, the ratio between specialized pro-resolving and pro-inflammatory mediators emerges as key issue in achieving resolution of inflammation.

Soluble mediators play a crucial role in controlling resolution of inflammation. Specifically, families of pro-resolving

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mediators (SPMs) have been shown to control resolution of inflammation. Key players consist of resolvins, protectins, and maresins that can stimulate self-limited innate responses and enhance innate microbial killing and clearance to protect organ structure and function [39–42]. SPMs thus may actively reprogram the inflammatory process and favor resolution of inflammation. In addition to SPMs, however, other soluble mediators such as cytokines may regulate resolution of inflammation. For instance, cytokines with anti-inflammatory immune function such as IL-10 and TGF-beta are frequently produced during inflammation by macrophages or lymphocytes, respectively [43–46]. In particular, regulatory T cells (Treg) produce such cytokines that actively suppress inflammatory processes and favor resolution of inflammatory processes [47, 48].

In some situations, chronic inflammation may not resolve because of an overwhelming pro-inflammatory immune response that overrides anti-inflammatory signals and mediators [38]. This pro-inflammatory response may involve the production and release of chemical mediators such as vasoactive amines (e.g., histamine), eicosanoids (e.g., leukotrienes), and small peptides (e.g., bradykinin) [49, 50]. Additionally, pro-inflammatory mediators comprise cytokines such as IFN-gamma, tumor necrosis factor (TNF), and IL-23 [26, 51–55]. They may amplify inflammatory processes by inducing cell death or activating other local immune cells in the microenvironment. Based on these findings targeting of such pro-inflammatory mediators and molecules has been tested in clinical trials and is now routinely used in various chronic inflammatory and autoimmune disorders [56–58]. Frequent intervention strategies in clinical routine include anti-TNF antibodies such as infliximab [58], adalimumab [59], certolizumab pegol [60], and golimumab [61], and some of these TNF blockers have been successfully used in disorders such as rheumatoid arthritis, psoriasis, and inflammatory bowel diseases (Crohn's disease, ulcerative colitis). Additionally, the IL-6R inhibitor tocilizumab was approved for therapy of rheumatoid arthritis [62]. Moreover, the BAff inhibitor belimumab has been studied in lupus erythematosus [63], while the B cell inhibitor rituximab [64] that targets the CD20 molecule has been used together with methotrexate for treatment of rheumatoid arthritis. In multiple sclerosis, the CD52 inhibitor alemtuzumab has been tested for clinical therapy [65]. Furthermore, blockers of IL-4, IL-5, or IL-13 signalling such as benralizumab, mepolizumab, or dupilumab [66–70] have been used in patients with allergic asthma. In addition, monoclonal antibodies targeting IL-12/IL-23 p40 (e.g., ustekinumab in psoriasis and Crohn's disease [71–73]) or IL-23 p19 (e.g., risankizumab, guselkumab, tildrakizumab in psoriasis [74, 75]) have reached clinical therapy in a variety of inflammatory disorders. New approaches for therapy of inflammation came by studying immune cell trafficking [76, 77]. In fact, drugs blocking immune cell homing into inflamed tissues such as the alpha4/beta7 integrin blocker vedolizumab are nowadays routinely used for therapy of inflammatory bowel diseases. This drug prevents lymphocyte homing to the inflamed mucosa with subsequent immune cell activation and retention. Finally, S1P1 receptor agonists (e.g., ozanimod) have been shown to control immune cell efflux from lymph nodes and have been tested in multiple sclerosis [78–80]. Collectively, these findings suggest that selective immune cell intervention may block pro-inflammatory immune processes and foster resolution of inflammation. Novel therapies may allow better therapy of chronic inflammatory diseases and permit to address harder endpoints in clinical trials such as mucosal healing on endoscopy or even histological healing in ulcerative colitis [81, 82]. However, it should be noted only subsets of patients will respond to immunotherapy and thus development of biomarkers or other predictive parameters will be essential to allow personalized medicine in inflammatory disorders. Moreover, marked differences in immunotherapies exist between individual disorders. For instance, while anti-IL-17A blockers such as secukinumab were effective in psoriasis [20], they aggravated mucosal inflammation in patients with Crohn's disease [83] highlighting the concept of tissue-specific mechanisms affecting resolution of inflammation.

In the future, we may expect optimized immunotherapies with new small molecules or antibodies inducing clinical remission or full resolution of inflammation. Evidence in recent years has suggested that targeting several pro-inflammatory pathways simultaneously may be helpful in improving response to therapy. Potential examples include combination therapies of various biological agents, bispecific antibodies with dual targets or inhibitors of Janus kinases that target signalling events via a large number of cytokine receptors [84–86]. In addition, we need more insights into the anti-inflammatory signalling pathways to design more efficient pathways. Potential concepts in this context include administration of pro-resolving molecules, small chemical compounds triggering anti-inflammatory pathways or anti-inflammatory cytokines [26, 41]. These concepts might also be combined with the above approaches aiming at suppression of pro-inflammatory mediators in order to further optimize clinical therapy of inflammation.

Thus, various established strategies exist to foster the resolution process in chronic inflammatory disorders. In addition, numerous new concepts have entered preclinical studies or early clinical trials and may be used to boost resolution of inflammation in chronic inflammatory and autoimmune disorders in the future.

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