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REVIEW

Resolution of inflammation in arthritis

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Abstract
Rheumatoid arthritis is among the most frequent and severe chronic inflammatory diseases. The disease is characterized by ongoing synovial inflammation, which leads to the destruction of cartilage and bone. In RA, the mechanisms of resolution of inflammation, which are normally intact in the joints, are either suppressed or overruled. Little efforts have been undertaken to understand the mechanisms of resolution of arthritis until recently, when several molecular mechanisms have been identified that determine the chronicity and resolution of inflammation in the joints, respectively. This review describes the key concepts of resolution of arthritis mentioning the key mechanisms involved, such as regulatory macrophages, pro-resolving lipid, fatty acid and cytokine mediators, aggregated neutrophil extracellular trap formation, antibody glycosylation changes, and stromal cell alterations that are involved in determining the decision between chronicity and resolution of arthritis. Each of these mechanisms represents a potential therapeutic approach that allows skewing the balance of the inflammatory processes towards resolution.

Introduction

Inflammation of the joints (arthritis) is usually spurious and often occurs in the context of infection. If chronic, however, arthritis represents a severe condition that leads to the destruction the affected joints and increasing disability. Rheumatoid arthritis (RA) is the prototype example of a chronic inflammatory joint disease, which shows little probability to resolve spontaneously and usually requires life-long control of inflammation by anti-rheumatic drugs [1]. These observations suggest at the one hand joints bear very solid intrinsic resolution processes that prevent the development of chronic arthritis. On the other hand, chronic arthritis, like RA, may only develop if such resolution mechanisms are actively shut down or overwhelmed [2]. In the flowing chapters, the most important mechanisms of resolution of inflammation will be discussed (Fig. 1).

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The inner pro-resolving macrophage membranes in the joint

The natural capacity of joints to resolve and prevent inflammation in joints appears to be substantial. Given that joints are places of mechanical stress and continuous production of disease-associated molecular patterns (DAMPS), not lastly because of permanent wear and tear of the cartilage and other articular structures, nature has built very effective mechanisms that contain inflammation in the joints. Viral infections often involve joint leading to spurious arthritis, but such inflammation is usually resolved within days. Joints are maintained as immune privilege sites allowing virtually no or at best very limited entry of immune cells to the synovial fluid allowing the maintenance of locomotion due to a cell-free viscous synovial fluid. In fact, chronic arthritis can be seen as the rare exception from the rule and indicates that the natural resolution mechanisms in the joints are outmaneuvered or just simply overloaded. Very recent data have provided evidence that the inner surface of the joints is characterized by a membrane of phagocytizing resident macrophages that ascertain local pro-resolving function in the joints [3]. These surface macrophages form a barrier between the synovial fluid and the synovial tissue preventing cells to enter the fluid and trigger arthritis. Furthermore, this barrier has robust phagocytic functions, permitting it to sample and neutralize danger signals from the synovial fluid and, in case of arthritis, taking them up and clearing cells or their remnants from the synovial fluid which allows resolution of inflammation. To accomplish

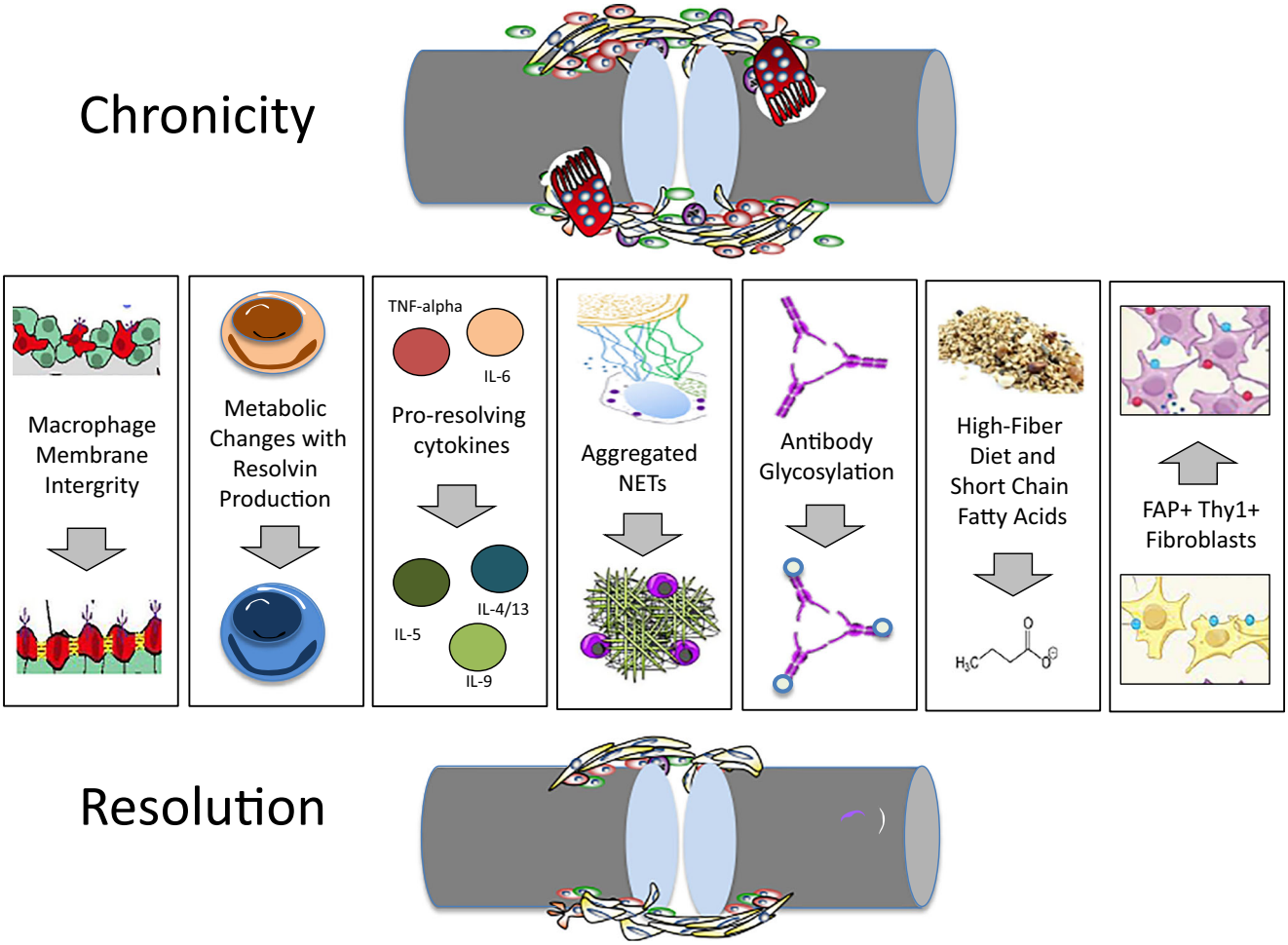

Fig. 1 Mechanisms of resolution of inflammation in arthritis

these function, resident macrophages on the surface of the synovial membrane ("lining macrophages") express tight junction proteins to seal the surface and additionally express proteins that mediate phagocytosis such as the TAM protein Axl, the "eat-me" signal milk-fat globule EFG-factor 8 (MFGE8) and TREM2, a surface receptor with yet unknown ligand that is involved in the containment of inflammation across different organs.

Pro-resolving lipid mediators

A central step in the process of resolution of inflammation is the stop of neutrophil and monocyte influx into the inflamed tissues and the removal of already existing immune cells in the affected tissues. Among others, small-molecule lipid mediators such as resolvins orchestrate this process [4]. It is hypothesized that changes in macrophage function occur during the switch from active to resolving inflammation, which go hand in hand with changes in immune metabolism in these cells [5, 6]. As part of these changes, lipid synthesis pattern shift in macrophages towards pro-resolving lipids such as lipoxin A2 and resolvins [5]. Furthermore, commonly used anti-rheumatic drugs such as non-steroidals and glucocorticoids can foster this shift towards pro-resolving lipids [7]. Based on these findings, it has been hypothesized that in chronic arthritis, such as RA, there might be under-functioning of pro-resolving lipid mediators. Such scenario could be based on a failure to switch macrophage metabolism from a pro-inflammatory cytokine–producing phenotype to a pro-resolving phenotype. Supporting evidence for such concept comes from animal and human studies on resolvin D3, for instance, levels of which are low in the joints of mice with chronic arthritis as well as in the serum of humans with RA [8]. Conversely, therapeutic supplementation of resolvin D3 in mice reduced the influx of immune cells to the joints and promoted resolution of arthritis in experimental models [8].

Pro-resolving and anti-inflammatory cytokines in arthritis

Cytokines are predominantly known for their pro-inflammatory role in arthritis, with TNF-alpha and IL-6 the

key mediators of inflammation in RA [9]. These cytokines orchestrate synovial inflammation by affecting the influx of innate immune effector cells to the joints, promoting angiogenesis and triggering cartilage and bone destruction. While the nature of the key pro-inflammatory mediators in RA is known since many years, the concept that pro-resolving and anti-inflammatory cytokines exist that promote the resolution the disease is rather novel. Above all, IL-9 has been identified as a potent pro-resolving cytokine that limits inflammation in experimental arthritis and human RA [10]. IL-9 is part of the type 2 immunity cytokines and serves as growth factor for innate lymphoid cells type2 (ILC2), which can engage and activate regulatory T cells and thereby limit inflammation. It has been show that ILC2 numbers augment during the resolution phase of arthritis, while being very low during the active phase of the disease. These cells not only constitute a major source of IL-9 in the joint but are also regulated by IL-9 triggering their expansion. IL-9 activates regulatory T cells in a cell-cell contact GITRL- and ICOSL-dependent manner and thereby suppresses T cell activation and promotes resolution of arthritis. Apart from IL-9, also other mediators of type 2 immunity are supporting resolution of arthritis: IL-4 and IL-13, for instance, which are involved in asthma and atopic dermatitis, have an essentially different role in arthritis. Both cytokines limit inflammation by expanding IL-10-producing regulatory macrophages in a STAT6-dependent manner [11]. As such, IL-4 and IL-13 promote the resolution of inflammation. In line with this concept, also IL-5, the key cytokine–promoting eosinophils, has pro-resolving functions in arthritis [11]. It has been shown that deficiency of IL-5 increases the severity of arthritis, while increased eosinophils inhibit arthritis. Notably, eosinophil numbers significantly increase in the joints during the resolution phase of arthritis suggesting their functional importance in stopping joint inflammation. Overall these data suggest that cytokines mediating type 2 immunity are negative regulators of arthritis and promote resolution of the disease.

Aggregation of neutrophil extracellular traps

Trapping and degradation of pro-inflammatory cytokine is another resolution mechanism in arthritis. This mechanism is primarily revisited in gouty arthritis, which is characterized by rather fast and often spontaneous resolution of joint inflammation. Functionally trapping and degradation of cytokines is accomplished by the aggregation of neutrophil extracellular traps (NETs), which provides a microenvironment rich in proteases that cleaves inflammatory cytokines, and hence allows a sharp and fast drop in local cytokine concentration with the consequence of resolution of arthritis [12]. Aggregated NET-based cytokine trapping and resolution of inflammation, however, requires large neutrophil concentrations that are achieved in gout and bacterial infections but are probably not reached in the case of synovial inflammation in RA. Hence, it is likely, the aggregated NETs play only a role in certain forms of arthritis, particularly those with high-level neutrophil influx. Conversely, if NETs are not becoming aggregated, they can provide a source of neoantigens such as citrullinated proteins, which can initiate and/or maintain autoimmunity in RA [13].

Modulation of antibody glycosylation

Pro-inflammatory effector functions of autoantibodies may be another reason for lack of resolution of RA. Rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) are present in the majority of RA patients and considered being involved in inflammatory disease process. Both antibody species precede the onset of RA and epitope spreading and increase in their levels occurs just before the clinical phase of RA starts [14]. Furthermore, these antibodies do usually not disappear if RA is treated with anti-inflammatory drugs [15]. While RF is an immune complex, ACPA can form immune complexes allowing effective binding to FC-receptors on monocyte/macrophages leading to their activation and the release of cytokines. This effector function of antibodies is regulates by glycosylation at their Fc-part, which modulates their binding to Fc-receptors [16]. While high glycosylation inhibits antibody effector function and promotes resolution of arthritis, low glycosylation of the Fc-part of autoantibodies promotes effector function, cytokine release from the target cell and inflammation [17]. Influencing the glycosylation of antibodies may be one option to promote resolution of arthritis. For instance, experimental ingestion of the sugar Mannac, which is a substrate for the enzymes adding sugars to the Fc portion of immunoglobulins, is not only increasing the glycosylation of antibodies but also mitigates inflammation in arthritis [18].

Pro-resolving gastrointestinal metabolites

Short-chain fatty acids are produced from the cleavage of dietary fibers by microbial organisms residing in the colon. The generation of these metabolites is dependent on fiber-rich diet but also by the composition of microbial species in the gut. Changes in the diet or intestinal dysbiosis can alter the production of short-chain fatty acids and impair gastrointestinal barrier function. Importantly, short-chain fatty acids have shown to be important anti-inflammatory molecules that promote the resolution of inflammation in arthritis [19]. Hence, treatment with short-chain fatty acids or ingestion of fiber-rich diet mitigates arthritis and could emerge as a dietary approach to promote resolution of disease. In addition to that, short-chain fatty acids beneficially affect bone homeostasis in the joints, which provides an additional support for resolution of arthritis [20].

Stromal cell function influencing resolution of inflammation

Resolution of inflammation in arthritis may be also guided by resident tissue responses. In the joints, fibroblasts reside in the synovial tissue and contribute to cytokine (such as IL-6) and chemokine production in arthritis. Furthermore, epigenetic imprinting of fibroblasts occurs in RA, which may contribute to continuous cytokine production by these resident cells overcoming resolution of inflammation [21]. Recent advances of characterization of fibroblasts in the joints have shown that fibroblast positive for fibroblast-activating protein (FAP) and Thy-1 are able to continuously produce cytokines and chemokines at the local level, and thereby effectively prevent resolution of inflammation [22]. Targeting such cells could stimulate resolution of arthritis and prevent the rather high relapse rate of the disease when tapering anti-inflammatory treatment.

Summary

Remarkable progress has been achieved to better understand the resolution of arthritis. Apart from lipid mediators, also specific cytokines, such as IL-9 and IL-5 trigger pro-resolving actions in arthritis and are linked to specific immune cells such as ILC2 and eosinophils, respectively, that are involved in the resolution process. Furthermore, sugar metabolism effectively controls the inflammatory potential of antibodies, while fatty acid metabolism is a key determinant for gastrointestinal barrier function and systemic inflammation in arthritis. Finally, changes in the stromal cell compartment, some of them induced by epigenetic changes, also influence resolution of arthritis. Some of these pathways appear to provide excellent opportunities for disease modulation in inflammatory joint diseases such as RA, developing an approach to foster and/or restore resolution of inflammation.

Compliance with ethical standards

Conflicts of interest The author declares that there are no conflicts of interest

References

1. McInnes IB, Schett G (2011) The pathogenesis of rheumatoid arthritis. New Engl J Med 365:2205–2219
2. Schett G, Neurath MF (2018) Resolution of chronic inflammatory disease: universal and tissue-specific concepts. Nat Commun 9: 3261
3. Culemann S, Grüneboom A, Nicolás-Ávila JÁ, Weidner D, Lämmle KF, Rothe T, Quintana JA, Kirchner P, Krljanac B, Eberhardt M, Ferrazzi F, Kretzschmar E, Schicht M, Fischer K, Gelse K, Faas M, Pfeifle R, Ackermann JA, Pachowsky M, Renner N, Simon D, Haseloff RF, Ekici AB, Bäuerle T, Blasig IE, Vera J, Voehringer D, Kleyer A, Paulsen F, Schett G, Hidalgo A, Krönke G (2019) Locally renewing resident synovial macrophages provide a protective barrier for the joint. Nature. 572:670–675
4. Serhan CN (2014) Pro-resolving lipid mediators are leads for resolution physiology. Nature 510:92–101
5. Levy BD, Clish CB, Schmidt B, Gronert K, Serhan CN (2001) Lipid mediator class switching during acute inflammation: signals in resolution. Nat Immunol 2:612–619
6. O'Neill LA (2015) A broken krebs cycle in macrophages. Immunity 42:393–394
7. Perretti M, Chiang N, La M, Fierro IM, Marullo S, Getting SJ, Solito E, Serhan CN (2002) Endogenous lipid- and peptide-derived anti-inflammatory pathways generated with glucocorticoid and aspirin treatment activate the lipoxin A4 receptor. Nat Med 8: 1296–1302
8. Arnardottir HH, Dalli J, Norling LV, Colas RA, Peretti M, Serhan CN (2016) Resolvin D3 is dysregulated in arthritis and reduces arthritic inflammation. J Immunol 197:2362–2368
9. Schett G, Elewaut D, McInnes IB, Dayer JM, Neurath MF (2013) How cytokine networks fuel inflammation: toward a cytokine-based disease taxonomy. Nat Med 19:822–824
10. Rauber S, Luber M, Weber S, Maul L, Soare A, Wohlfahrt T, Lin NY, Dietel K, Bozec A, Herrmann M, Kaplan MH, Weigmann B, Zaiss MM, Fearon U, Veale DJ, Cañete JD, Distler O, Rivellese F, Pitzalis C, Neurath MF, McKenzie A, Wirtz S, Schett G, Distler JHW, Ramming A (2017) Resolution of inflammation by interleukin 9 producing type 2 innate lymphoid cells. Nat Med 23:938–944
11. Chen Z et al (2016) Th2 and eosinophil responses suppress inflammatory arthritis. Commun. 7:11596
12. Schauer C, Janko C, Munoz LE, Zhao Y, Kienhöfer D, Frey B, Lell M, Manger B, Rech J, Naschberger E, Holmdahl R, Krenn V, Harrer T, Jeremic I, Bilyy R, Schett G, Hoffmann M, Herrmann M (2014) Aggregated neutrophil extracellular traps limit inflammation by degrading cytokines and chemokines. Nat Med 20:511–517
13. Khandpur R, Carmona-Rivera C, Vivekanandan-Giri A, Gizinski A, Yalavarthi S, Knight JS, Friday S, Li S, Patel RM, Subramanian V, Thompson P, Chen P, Fox DA, Pennathur S, Kaplan MJ (2013) NETs are a source of citrullinated autoantigens and stimulate inflammatoryresponses in rheumatoid arthritis. Sci Transl Med 5: 178ra40
14. Malmström V, Catrina AI, Klareskog L (2017) The immunopathogenesis of seropositive rheumatoid arthritis: from triggering to targeting. Nat Rev Immunol 17:60–75
15. Wunderlich C, Oliviera I, Figueiredo CP, Rech J, Schett G (2017) Effects of DMARDs on citrullinated peptide autoantibody levels in RA patients-a longitudinal analysis. Semin Arthritis Rheum 46(6): 709–714
16. Nimmerjahn F, Ravetch JV (2007) The antiinflammatory activity of IgG: the intravenous IgG paradox. J Exp Med 204:11–15
17. Pfeifle R, Rothe T, Ipseiz N, Scherer HU, Culemann S, Harre U et al (2017) Regulation of autoantibody activity by the IL-23-T_H17 axis determines the onset of autoimmune disease. Nat Immunol 18:104–113
18. Harre U, Lang SC, Pfeifle R, Rombouts Y, Fruhbeisser S, Amara K, Bang H, Lux A, Koeleman CA, Baum W et al (2015) Glycosylation of immunoglobulin G determines osteoclast differentiation and bone loss. Nat Commun 6:6651
19. Lucas S, Omata Y, Hofmann J, Böttcher M, Iljazovic A, Sarter K, Albrecht O, Schulz O, Krishnacoumar B, Krönke G, Herrmann M, Mougiakakos D, Strowig T, Schett G, Zaiss MM (2018) Short-chain fatty acids regulate systemic bone mass and protect from pathological bone loss. Nat Commun 9:55

20. Zaiss MM, Jones RM, Schett G, Pacifici R (2019) The gut-bone axis: how bacterial metabolites bridge the distance. J Clin Invest 129:3018–3028
21. Frank-Bertonceli M, Trenkmann M, Klein K, Karouzakis E, Rehrauer H, Bratus A, Kolling C et al (2017) Epigenetically-driven anatomical diversity of synovial fibroblasts guides joint-specific fibroblast functions. Nature Comm 8:14852
22. Croft AP, Campos J, Jansen K, Turner JD, Marshall J, Attar M, Savary L, Wehmeyer C, Naylor AJ, Kemble S, Begum J, Dürholz K, Perlman H, Barone F, McGettrick H, Fearon DT, Wei K, Raychaudhuri S, Korsunsky I, Brenner MB, Coles M, Sansom SN, Filer A, Buckley CD (2019) Distinct fibroblast subsets drive inflammation and damage in arthritis. Nature. 570:246–251