Review

Pathogenesis of rheumatoid arthritis: one year in review 2022

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ABSTRACT

The mechanisms underlying the pathogenesis of rheumatoid arthritis (RA) involve different components of the immune system. In subjects with genetic predisposition to develop RA, a tight interaction between cells and mediators of the innate and adaptive immune system leads to the amplification and perpetuation of inflammation and tissue remodelling. The research carried out in the last year in the field of RA has improved the current knowledge on the pathogenesis of the disease, and is potentially useful to develop new therapeutic approaches. Thus, in this review we provide an overview on the new insights into RA pathogenesis, resulting from a literature search of the data published in the last year.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by a tight interaction between cells and mediators of the innate and adaptive immune system. It is well known that this interaction leads to the development of local as well as of systemic inflammation at different steps of the disease (1, 2). In the last year, particular advances have been made in the mechanisms involving cells of both the innate immune system, such as monocytes and macrophages, and the adaptive counterpart, such as B and T lymphocytes. Several soluble and membrane-bound mediators play relevant roles in this cross-talk by orchestrating different inflammatory and tissue remodelling pathways. The technological progress has made it possible to better characterise these cellular and molecular processes, which could potentially lead to the identification of new therapeutic targets in RA. In this review article we have summarised the results of a Medline search of original research articles in English published in the PubMed database from January 1 to December 31, 2021.

Genetic aspects

During the last decades, great progress has been made in understanding the genetic aspects of RA, mainly due to the remarkable progress in genotyping technology and the successful application of genome-wide association studies (GWAS).

Several genetic polymorphisms in the major histocompatibility complex (MHC) genes, divided into class I (HLA-A, B, C), class II (HLA-DR, DP, DQ), and class III sub-regions, have been associated with RA susceptibility. In particular, HLA-DRB1 locus was reported to be crucial in RA pathogenesis, by encoding for the MHC class II antigen-presenting molecules. Among HLA-DRB1 loci, the HLA-DRB1*04 and HLA-DRB1*01 alleles seem to increase the risk of developing RA (3), and the HLA-DRB1*04:01 allele was associated with anti-a501-515cit antibody positivity (4). In parallel, the HLA-B*08 allele was specifically associated with serum positivity of anti-carbamylated protein antibodies (5), proving its major role in RA susceptibility and being widely investigated in the last few years (6, 7). Notably, it should be taken into account that HLA alleles could also predict the therapeutic response to biological agents in RA patients: for example, HLA-DRB1*0404 allele may predict the clinical response to anti-tumour necrosis factor (TNF)-α drugs (8).

In addition to the well-recognised role of HLA susceptibility loci in RA, a number of genetic variants in non-HLA loci have been implicated in the heritability of the disease. This is the case of genetic polymorphisms of pro-inflammatory cytokines and cytokine receptor genes playing relevant roles in RA susceptibility and progression of the disease. Among the different cytokines orchestrating RA pathogenesis, IL-6 is a key cytokine in the development

and progression of the disease. In this regard, a number of polymorphisms (rs184229712, rs36215814, rs2069837, and rs1800796) of the IL-6 gene have been recently associated with RA genetic susceptibility (9,10). Likewise, IL-1 also contributes to the mechanisms underlying RA pathogenesis and it exerts its biological functions by binding the signalling receptor IL-1 receptor 1 (IL-1 R1). It has been recently proven that rs3917318, rs956730 and rs1049057, SNPs of IL1R1 gene, correlate with RA susceptibility in the Chinese Han population (11).

Among the potential non-HLA susceptibility genes, the IL-1 R-associated kinase (IRAK1) gene is involved in different processes that are important for the activation of innate and adaptive immune responses, and it has been shown that one of its alleles, the rs1059703 T allele, affects the risk of developing RA and is related to the severity of the disease (12).

In addition, an aberrant expression of IL-35, a newly discovered IL-12 family member, was observed in RA. In this regard, the IL-35 gene polymorphisms rs2227314, rs2243131, rs9807813, and rs583911 were found to impact on RA susceptibility risk in a Chinese Han population (13). Several experimental reports have also suggested an essential role of IL-21 in RA pathogenesis, due to the crucial function of this mediator in the regulation of both the innate and adaptive immune systems. Notably, IL-21 gene polymorphism rs2055979 was recently associated with disease susceptibility and activity in a Chinese cohort of RA patients (14).

Over the last few years, increasing attention has also been given to novel genes encoding for signalling regulating molecules. In this regard, CD40, a member of the TNF family of transmembrane glycoproteins expressed on the surface of different cells, acts as a potent T-cell co-stimulatory factor. The co-dominant and dominant models of rs1569723, rs1883832 and rs4810485 polymorphisms of CD40 gene have been recently associated with increased susceptibility to RA in a Chinese Han population (15). Furthermore, CD209 was reported to regulate the monocyte-induced T-cell activation and to modulate the adaptive immune response in RA synovial tissue. A novel variant -96C>A in CD209 gene promoter was identified as a potential disease susceptibility factor in the Taiwanese population (16). In parallel to the T signalling regulating molecules, also those regulating B-cell signalling, including the new member of the Ig superfamily Fc receptor-like (FCRL) gene family, were recently investigated. Among the FCRL gene family, FCRL1 rs2050568, FCRL3 rs2317230, and FCRL6 rs58240276 polymorphisms were found to be associated with RA susceptibility in the Chinese Han population (17).

In parallel to HLA and non-HLA loci, accumulating evidence suggests that epigenetic mechanisms, including DNA methylation, small (s) and long (l) non coding RNAs (ncRNAs), play a crucial role in RA pathogenesis. For example, Podgórska *et al*. demonstrated that the level of ADAMTSL2 and LRPAP1 gene methylation might impact on RA susceptibility and disease activity (18). Among the sncRNAs, micro-RNAs (miRNAs) can regulate gene expression mainly through combining with the 3´untranslated regions (3´UTRs) of target messenger RNA (mRNA).

Altered expression levels of a number of miRNAs, including miR-22-3p, miR-26b-5p, miR-142-3p, and miR-155 have been also confirmed in RA patients (19). Moreover, serum expression of miR-224, miR-760, miR-483-5p, miR-378 and miR-375 was found to be significantly upregulated and it seems to correlate with the DAS28 score in RA patients (20), while miRNA-22 appears to be associated with disease activity in well-established RA (21). In addition, several upregulated (hsa-miR-187-5p, -4532, -4516) and downregulated (hsa-miR-125a-3p, -575, -191-3p, -6865-3p, -197-3p, -6886-3p, -1237-3p, -4436b-5p) differentially expressed miRNAs were identified in the serum of naive active RA patients (22), but their functional roles are not well defined. Recently, a down-regulation of several miRNAs (*e.g*. miR-140-3p, miR-137 and miR-449) with a protective role towards the development of RA has been shown. Following the down-regulation of these miRNAs, different mechanisms are enhanced, including proliferation and migration of synovial fibroblasts (SF), as well as inhibition of their apoptosis (23-25). Importantly, the definition of how some epigenetic modifications are linked to specific clinical aspects of the disease is a relevant and timely challenge. In this regard, the following miRNAs, let-7c-5p, miR-30e-5p, miR-4446-3p, miR-126-5p, miR-3168, miR-425-5p, miR-126-3p, miR- 30a-5p, and miR-125a-5p, seem to be associated with the development of coronary atherosclerosis in patients with RA (26).

In parallel to miRNAs, lncRNAs are also major epigenetic modifications. It has been proven that these RNA transcripts, with lengths exceeding 200 nucleotides, play important roles in RA pathogenesis by acting at different ways. For instance, lncRNAS56464.1 (27) and linc00152 (28) are involved in RA pathogenesis by regulating proliferation and inflammatory response of SF, respectively. In addition, they are able to act as competing endogenous RNAs combining with miRNAs and impairing their effects on their targeted transcripts. For example, lncRNA SNHG14 enhances the production of pro-inflammatory cytokines by targeting the miR-17-5p/misshapen like kinase 1 (MINK1) axis and by activating the jun N-terminal kinase (JNK) signalling pathway (29). Moreover, lncRNA NEAT1 may regulate the proliferation and production of inflammatory cytokines by SF, mainly by targeting miR-204-5p (30), while lncRNA FOXD2-AS1 seems to promote SF proliferation and invasion by regulating the miR-331-3p/PIAS3 axis (31). On the other hand, some lncRNAs, such as lncRNA growth arrest-specific 5 (GAS5), may be protective by regulating miR-222-3p/sirtuin 1 (Sirt1). This lncRNA is down-regulated in RA patients (32).

Circular RNAs (circRNAs), a subclass of closed lncRNA that binds miRNAs and reduces their activity, have also been recently investigated in RA. Several circRNAs have been recognised as important regulators of RASF. Among them, circRNA fragile mental retardation 2 (circ-AFF2) expression is enhanced in

Table I. Genetic aspects involved in the pathogenesis of RA.

Genetic features	Associations or roles	References
HLA-DRB1*04	Susceptibility	(3)
HLA-DRB1*01	Susceptibility	(3)
HLA-DRB1*04:01	Anti-a501–515cit antibodies positivity	(4)
HLA-B*08	Anti-carbamylated protein antibodies positivity	(5)
IL-6 (rs184229712, rs36215814, rs2069837, rs1800796)	Susceptibility	(9)
IL-1R1 (rs3917318, rs956730, rs1049057)	Susceptibility	(11)
IRAK1 (rs1059703 T allele)	Susceptibility and disease severity	(12)
IL-35 (rs2227314, rs2243131, rs9807813, and rs583911)	Susceptibility	(13)
IL-21 (rs2055979)	Susceptibility and disease activity	(14)
CD40 (rs1569723, rs1883832, and rs4810485)	Susceptibility	(15)
CD209-96A variant	Susceptibility	(16)
MiRNA-22	Disease activity	(21)
lncRNAS56464.1	Susceptibility	(27)
linc00152	Susceptibility	(28)
lncRNA SNHG14	Susceptibility	(29
lncRNA NEAT1	Susceptibility	(30)
lncRNA FOXD2-AS1	Susceptibility	(31)
circ-AFF2	Susceptibility	(33, 34)
circMAPK9	Susceptibility	(35)
Circ_0088194	Susceptibility	(36)

RA synovial tissue, where it may promote proliferation, migration, invasion and pro-inflammatory activities of SF (33, 34). In addition, circMAPK9 was found to promote pro-inflammatory activities of SF via regulating the miR-140-3p/ protein phosphatase magnesium-dependent 1A (PPM1A) axis (35). Finally, the newly discovered circRNA Circ_0088194 has been associated with disease activity in RA by promoting invasion and migration of SF following its binding to miR-766-3p and consequent increased expression of matrix metalloproteinase 2 (MMP2) (36). The novel achievements on the genetic aspects involved in RA pathogenesis are summarised in Table I.

Take home messages

- HLA-B*08 allele may be associated with serum positivity of anti-carbamylated protein antibodies in RA (5).
- Novel genes encoding for T and B cells signalling regulating molecules have been recently associated with RA susceptibility (15-17).
- let-7c-5p, miR-30e-5p, miR-4446-3p, miR-126-5p, miR-3168, miR-425-5p, miR-126-3p, miR- 30a-5p, and miR-125a-5p were associated with coronary atherosclerosis in RA patients (26).
- CircRNAs (circ-AFF2, circMAPK9 and Circ_0088194) were recently identified as important regulators of SF in RA (33-36).

Innate immune response

Over the last few years, the critical role of the innate immune system in RA pathogenesis has been extensively investigated. Cells and soluble mediators of the innate immune system play a key role in non-specific recognition of pathogens and represent the first defence against microbes. However, the dysregulation of this system may contribute to the amplification and perpetuation of inflammation with joint damage in RA.

Innate immune cells may be activated by a large number of specialised receptors, including toll-like receptors (TLRs), recognising either pathogen-associated molecular patterns expressed by microbial pathogens or damage-associated molecular patterns expressed by stressed cells.

Altered TLR-mediated response may play a crucial role in RA pathogenesis. Differences in their expression patterns in the synovial tissue of seronegative compared to seropositive RA patients have been recently reported. In particular, the expressions levels of TLR 1, 4 and 8 were found to be increased in seropositive RA (37). Multiple factors can affect TLR-induced inflammatory responses in this disease. For example, endoplasmic reticulum (ER) stress and its regulator, X-box-binding protein-1 (XBP-1), may act in conjunction with TLRs in driving the inflammatory response of SF (38).

Synovial tissue resident cells, such as SF play a pivotal role in RA pathogenesis. In this regard, activated SF are known to promote inflammation and joint destruction by infiltrating articular cartilage and releasing several mediators, including cytokines, chemokines and MMPs, and ultimately promote the remodelling of extracellular matrix and cartilage. Among these inflammatory mediators, *in vitro* experiments showed that the chemokine C-C motif ligand (CCL) 11 secreted by SF following TNF-α stimulation binds to its receptor C-C chemokine receptor (CCR) 3 expressed in SF, increasing in turn its autocrine production and CCR3 expression in these cells (39). The self-amplification mechanism of CCL11 via CCR3 may contribute to the amplification of inflammation and pro-fibrogenic effects of SF. In parallel, TNF-α may also promote the interaction between these structural cells and B cells, by enhancing human vascular cell adhesion molecule-1 (VCAM-1) expression in SF via human B cell-activating factor (BAFF) production and JNK activation (40).

In the scenario of inflammation and remodelling in RA, an important role is also played by pro-angiogenic mechanisms.

Intriguingly, the expression of pro-inflammatory cytokines such as IL-17A IL-6 and TNF-α and the pro-angiogenic mediator vascular endothelial growth

factor (VEGF) with hypoxia-inducible factor-1α (HIF-1α) was found to be markedly up-regulated in SF, upon IL-34 stimulation (41). Methyltransferase-like 3 (METTL3), a crucial component of the N6-methyladenosine (m6A) methyltransferase complex, is also able to induce SF activation and an inflammatory response via triggering the NF-κB signalling pathway (42). Monocyte chemoattractant protein-1 (MCP-1), a key chemoattractant mediator for monocytes also known as CCL2, has been recently reported to promote proliferation and migration of SF and to inhibit their apoptosis in collagen-induced RA rat model (43). Furthermore, acid sphingomyelinase that is significantly increased in the sera of RA patients, may play a pathogenic role by regulating IL-6 synthesis, and SF proliferation, migration, and invasive capacity (44). Recently, the transient receptor potential canonical 6 (TRPC6), a cation channel involved in regulating Ca^{2+} dynamics especially during G protein-coupled receptor signalling, has been reported to be increased in SF from mice with collagen induced arthritis (CIA), but its roles need to be further investigated (45).

Besides structural resident cells, it is well recognised that cells of the innate immune system such as monocytes may orchestrate joint inflammation in RA. Based on the expression of CD14 and CD16, monocyte subpopulations can be classified into classical (CD14++CD16-), intermediate (CD14++CD16+/++) and nonclassical (CD14-/+CD16++) monocytes. Differences in monocytes subpopulations, with a shift from classical to pro-inflammatory intermediate and nonclassical forms, have been recently shown in individuals at high risk of developing RA (46). In this context, McGarry et al. demonstrated in RA that circulating CD14+ monocytes display a pro-inflammatory and hyper-metabolic phenotype, regulated by signal transducer and activator of transcription 3 (STAT3) signalling (47).

The expression of monocyte membrane receptors may be altered during different stages of the disease. For example, increased expression levels of formyl peptide receptor 2 (ALX/FPR2) and leukotriene B4 receptor 1 (BLT1) were reported in CD14+ peripheral monocytes from low disease activity and remission status RA patients (48).

As observed for monocytes, macrophages play active roles in the initiation and perpetuation of RA. For example, macrophages for RA may be able to turn into a pro-inflammatory phenotype or directly differentiate into mature osteoclasts, promoting pannus formation in the presence of pro-inflammatory mediators, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) (49), IL-34 (50), or CCL25 (51).

Besides macrophages and monocytes, neutrophils are also believed to play an important role in both the initiation and progression of RA, in fact an expansion of activated neutrophils was reported in RA inflamed joints. Wright *et al*. recently described an altered neutrophil phenotype in RA synovial fluid, characterised by increased expression of chemokines and reactive oxygen species (ROS) production, delayed apoptosis, and activation of signalling cascades, regulating the production of neutrophil extracellular traps (NETs) (52).

Extracellular vesicles (EVs), microparticles released from various cells during cell activation and apoptosis, have also been recently implicated in the pathogenesis of RA. Elevated levels of circulating EVs of different cell origins were found in patients with established RA, in relation to the inflammatory parameters and coagulation activation (53).

Among the different components of the innate immune system, emerging data suggest a potential role of the innate lymphoid cells (ILCs) in the pathogenesis of RA. Since their identification as a peculiar leukocyte population, ILCs have been considered crucial in maintaining tissue homeostasis and bridging the innate and adaptive immune system. Based on their transcriptional regulation and cytokine profiles, ILCs can be classified into three subsets (ILC1, ILC2, ILC3) with defined phenotypes and functional profiles as well as T helper lymphocytes, their cellular counterpart in the adaptive immune system. Altered distribution and function of ILCs subsets have been observed in a variety of autoimmune diseases, including RA and CIA model, suggesting a potential pathogenetic roles of these cells. In particular, ILC1 proportions were reported to be decreased in patients with stable RA and positively correlated with disease activity. On the contrary, ILC2 were found to be increased in the peripheral blood of patients with stable RA and in immunised mice without arthritis, suggesting that these subpopulations of ILCs might play a protective role in the disease (54).

Growing attention has also been given to the role of dendritic cells (DCs) in the pathogenesis of the disease. Although DCs are reported to contribute to RA pathogenesis by promoting local infiltration of leukocytes, producing inflammatory mediators and presenting autoantigens to autoreactive T cells, relatively little is known about the mechanisms behind their involvement. In this regard, Yabe *et al*. demonstrated that T cell-interacting, activating receptor on myeloid cells-1 (TARM1), a newly identified member of the leukocyte Ig-like receptor family, plays an important role in the development of CIA, by promoting the maturation and activation of DCs (55). Moreover, TARM1 gene expression in DCs was reported to be enhanced by DCs-derived cytokines, suggesting that TARM1 may promote DCs maturation by a self-amplification loop mechanism.

Take home messages

- Seronegative and seropositive RA patients display different expression patterns of TLRs in the synovial tissue (37).
- IL-34, METTL3, MCP-1 and TRPC6 may critically modulate the activation and function of SF (41-43, 45).
- Circulating CD14+ monocytes display a pro-inflammatory and hyper-metabolic phenotype in RA (47).
- Dysregulation of different subpopulations of ILCs is reported in RA patients and CIA mice model (54).
- TARM1 may promote DCs maturation in RA by a self-amplification loop mechanism (55).

Adaptive immune response

Over the last year, several articles have explored the role of adaptive immunity in RA pathogenesis. Recently, the understanding of RA preclinical phase and in particular immunological analysis of first-degree relatives of RA patients gained increasing scientific interest. By means of next-generation sequencing of the TCR CDR3β repertoire, Lamacchia *et al*. demonstrated that highly expanded T cell clones (HEC) can be detected in the peripheral blood of subjects before the clinical onset of RA, and their levels seem to be higher in symptomatic *versus* asymptomatic RA first-degree relatives. In addition, they have shown that HEC levels increased over time (56).

When focusing on established RA, the larger bulk of studies concerns T lymphocytes, in particular certain sub-populations, including regulatory T cells (Treg).

With regard to Th1 lymphocytes, the PRECISE Systemic Autoimmune Diseases (PRECISESADS) multicentre, cross-sectional study demonstrated that a pro-inflammatory cytokine profile, defined by high levels of CXCL10, IL-6, IL-2, and TNF, is a peculiar signature in a subgroup of patients with RA as observed in systemic lupus erythematosus, Sjögren's syndrome and systemic sclerosis. These patients are characterised by a more severe disease and higher levels of autoantibodies, suggesting an uncontrolled pro-inflammatory Th1 immune response. Furthermore, B lymphocytes seem to be able to fuel the proliferation of naive T lymphocyte and to facilitate the commitment towards a Th1 phenotype (57).

In addition, another study demonstrated that activated Th1 cells might promote the generation of CXCL9/10-producing T-bet+ B cells. Furthermore, these newly generated B cells are then able to facilitate the migration of $CD4^{(+)}$ T cells, establishing a vicious circle leading to perpetuation of the mechanisms underlying disease pathogenesis (58).

Conflicting results were reported by two studies on the proportion of circulating Treg cells compared to normal subjects (59, 60). In fact, while one study described a reduction of Treg cells in RA, another one did not observe any differences between RA and control groups. However, in the latter study, an overall reduction of CD25 expression in circulating Treg cells was observed, suggesting a possible dysregulation of Treg homeostasis in the disease. It is now well established that not only Treg cells, but the balance of Treg and T effector cells, in particular T helper 17 (Th17) cells, plays an important role in the development and progression of RA. IL-6, one of the main cytokines involved in RA, was found to be able to drive Th17 cell differentiation by JAK-STAT3 signalling. Recently, the GRK2-A(3)AR-cAMP-PKA-CREB/ICER-RORγt pathway was also identified in experimental arthritis as responsible for IL-6 driven Th17 cell expansion (61). Furthermore, nucleotide-binding domain (NOD)-like receptor protein 3 (NLRP3) has been involved in Treg/Th17 cell balance as well as other members of the pro-resolving mediator (SPM) family, such as protectin DX (PDX) (62). In fact, studies on $NLRP3^{-/-}$ mice revealed that PDX could ameliorate the progression of experimental arthritis by restoring Treg/Th17 cell balance, via the inhibition of the NLRP3 inflammasome pathway. In parallel, another study aimed at clarifying the mechanisms underlying Treg/Th17 imbalance in RA, demonstrated that $CD4^{+}$ T lymphocytes from patients with RA and from mice with experimental arthritis have reduced phosphorylation of vasodilator-stimulated phosphoprotein (VASP), affecting integrin signalling and related pathways. In particular, integrin signalling is enriched in cells with low phosphorylation of VASP, and specific inhibition of p-VASP reduced the migratory function of Treg cells, but not that of effector T cells. By blocking IL-6R, which is highly expressed by Th17 cells, a restoration of phosphorylation level of VASP is achieved and ultimately this improved migration of Treg cells from RA patients (63).

With regard to cell migration, the involvement of the classical myokine myostatin (GDF-8) in the recruitment of Th17 cells to inflammatory sites has also been reported. This effect is linked to the modulation of CCL20 secretion by SF. In fact, *in vitro* studies demonstrated that myostatin plus IL-17 is able to enhance CCL20 secretion by structural cells. On the contrary, myostatin deficiency led to decrease the levels of this chemokine, with consequent reduction in migration of Th17 cells into the inflammatory site (64).

Based on the evidence that patients with RA display increased levels of IL-18 and decreased levels of its endogenous inhibitor IL-18 binding protein (IL-18BP), Min *et al*. demonstrated that RA peripheral blood and synovial fluid mononuclear cells treated with IL-18BP *in vitro*, displayed a more pronounced commitment towards a Treg cell phenotype and reduced Th17 cell phenotype differentiation (65). In parallel, they observed a reduction of both IL-17 and soluble receptor activator of nuclear factor kappa-B ligand (RANKL) levels, suggesting the role of IL-18BP in reducing IL-17-mediated osteoclastogenesis. On the contrary, cigarette smoking as well as aryl hydrocarbon receptor agonists was able to directly enhance IL-17 mediated osteoclastogenesis via the induction of microRNA-132 in Th17 cells. In fact, microRNA-132 induced osteoclastogenesis through the down-regulation of COX-2 (66). Finally, myeloid-derived suppressor cells (MDSCs), well recognised as inducers of the Th17 response in RA, were found to promote an osteoclastogenic phenotype in Th17 cells via the RANKL signalling (67).

With regard to Treg cells and osteoclastogenesis, a Treg cell population that displays an aberrant expression of RANKL and the capacity to drive RANKL-dependent osteoclast differentiation in addition to the usual suppressive capacity towards effector lymphocytes has been recently identified in RA synovial tissue. This population can be depleted in experimental arthritis following IL-1β blockade (68).

Plasma cells have also been investigated in the setting of osteoclastogenesis, revealing an increase of RANKL-expressing plasma cells in the bone marrow of mice with experimental arthritis. The genetic ablation of RANKL in B-lineage cells resulted in amelioration of periarticular bone loss, but not of articular erosion or systemic bone loss (69).

Recently, Patlan *et al*. showed that senescent T cells in RA, known as $CD4^+CD28$null cells, are preferentially polarised towards a Th17 rather than a Th1 phenotype (70), identifying a novel additional source of Th17 cells in RA. It has also been suggested that Th17 cells share similar differentiation pathways with Th9 cells. This implies that differentiation of these Th cells sub-populations might occur not only under Th9 inducing conditions, but also by a Th-17 polarising milieu. This was confirmed by recent *in vitro* studies in which exposing naive T cells, derived from normal subjects and RA patients, the differentiation of Th9 cells was also induced by Th17-driving conditions (71).

As far as follicular T helper (Thf) and Thf-like cells are concerned, segmented filamentous bacteria (SFB) are able to interact not only with gut Thf cells, but also with Thf cells located in other sites including joints. This was recently shown by using SFB in autoimmune arthritic K/BxN mice and demonstrating that SFB-induced arthritis was linked to the reduction of regulatory Thf cells' CTLA-4, hence gut microbiota distally impacts systemic autoimmunity by fine-tuning regulatory Thf cells (72). In addition, a new Thf-like cell subset expressing TLR4, producing IL-17, but not IL-21 and expanded in the synovial fluid of RA patients has been described (73). Programmed death-1 (PD-1) is a well-known surface marker typically expressed by Thf cells, however some studies identified novel $CD4^+$ T cell subsets expressing PD-1, but distinct from Thf cells. By investigating peripheral helper T cells (Tph) characterised by high surface levels of PD-1 it has been observed that these cells are able to produce a range of pro-inflammatory mediators, including TNF-α, IL-21 and CXCL13. T cells with this specific phenotype could be identified in the joint, but not in the peripheral blood of RA patients, and have been demonstrated to be autoreactive cells (74). In addition to $CD4^+$ cells, also a $CD8^+$ cell subset displayed high surface levels of PD-1 and other phenotypic features of Tph cells that can be found not only in the joints, but also in the peripheral blood of RA patients (75).

With regard to other newly identified T cell subsets, Zhao *et al*. described a $CD4^+$ population characterised by high expression of PD-1 and CXCR3, lacking of Treg and Thf markers such as FoxP3 and CXCR5. These cells are expanded in the peripheral blood of RA patients compared to normal subjects and this expansion mirrored disease activity (76). Likewise, stem cell-like memory T (Tscm) cells, a subset of memory T cells that have characteristics of stem cells, are expanded in RA and are more easily activated by anti-CD3/CD28 beads augmented by IL-6 compared to those isolated by normal subjects. These cells also displayed RA-specific transcriptome patterns detectable not only in patients with active disease, but also in those achieving remission. The latter finding suggests that Tscm cells may represent a source of pro-inflammatory mediators throughout the natural history of RA, regardless of the good clinical control of the disease (77).

As far as B lymphocyte subsets are concerned, a broad characterisation of seropositive RA B cell phenotype and their activities demonstrated that these cells secrete less IL-10 after *in vitro* activation, and they decreased their plasma cell differentiation frequency and IgM production. Furthermore, it has also been observed an increased number of atypical CD27-IgM-IgD-CD21- B lymphocytes (78), a reduced level of $CD19^+CD27^+CD24^{high}$ Breg cells with higher proportions of circulating $CD19^+CD27^+CD38^{high}$ plasmablasts (79).

Finally, with regard to autoantibodies and based on the knowledge that anti-modified protein antibodies (AMPA) IgG display cross-reactivity to multiple post-translational modifications, AMPA-IgM from RA patients were shown to exert the same cross-reactivity features of AMPA IgG and were also more potent then AMPA-IgG in complement-activation (80).

Take home messages

- Th1 cells might promote generation of CXCL9/10-producing T-bet+ B cells, that are able to facilitate the migration of $CD4^{(+)}$ T cells in RA (58).
- NLRP3 is involved in Treg/Th17 cell balance as well as PDX, a member of the pro-resolving mediator (SPM) family (62).
- GDF-8 is relevant for the recruitment of Th17 cells to inflammatory sites in RA (64).
- RA-T-cells, B-cells and plasmacells are able to drive RANKL-dependent osteoclast differentiation (68, 69).
- In RA CD27-IgM-IgD-CD21- B lymphocytes are increased while $CD19^+CD27^+CD24^{high}$ Breg cells with higher proportions of circulating $CD19^+CD27^+CD38^{high}$ plasmablasts are reduced (79).

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