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Physiology and Pathology of Autoimmune Diseases: Role of CD4+ T cells in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by synovial inflammation leading to bone erosion and to systemic manifestations in patients with long RA duration. Although the aetiology is unknown, several observations make currently clear that CD4 T cells play a key role in the pathogenesis: (1) RA associates with certain polymorphisms of HLA class II molecules, and (2) the repertoire and aging of CD4 T cells as well as the intracellular signalling mediating CD4 T cell activation are altered in RA patients. We describe herein the alterations found in CD4 T cells and the role of these cells in the development and progression of RA.

Keywords: autoimmunity, lymphocytes, synovitis, T cell signalling, T cell aging

1. Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease, which affects 0.33 to 2.65% of the population, showing differences between countries and studies [1–7]. It is more frequent in North America than Northern Europe, with Southern Europe having the lowest rate of incidence [8]. As other autoimmune diseases, RA is more prevalent in women than in men, suggesting that hormonal [9] and gender-related genetic factors [10] contribute to the development of the disease. RA is also more frequent in the elderly, consistent with a key role of immune system aging in this disease [11, 12].

RA physiopathology is characterised by persistent synovial inflammation that leads to joint deformity, stiffness and bone erosion. Consequently, patients suffer pain and progressive disability. Although the most evident feature of RA is synovitis, extra-articular manifestations of

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RA (ExRA) such as cardiovascular disease can be present in long-duration disease, raising the risk of early death [13, 14].

RA is associated to certain alleles of the major histocompatibility complex class II (MHC-II), and CD4 T cells of RA patients show abnormalities in intracellular signalling, repertoire and aging. It is then conceivable that CD4 T cells could be essential mediators in the development of the chronic inflammation occurring in RA. These cells are key regulators of the immune response secreting pro-inflammatory cytokines and cooperating with B cells for secreting antibodies. In fact, certain RA patients develop autoantibodies such as anti-citrullinated protein antibodies (ACPA) or rheumatoid factor (RF, which recognises the Fc portion of IgG), while other patients do not, indicating that RA comprises at least two different pathologies, seropositive and seronegative [15].

The study of CD4 T cell population has changed our understanding of RA: from the traditional paradigm, which considered that a small set of joint antigens causes the selective expansion of few antigen-specific cells, to a new model in which RA would be a systemic disease caused by alterations in T cell homeostasis and aging. In this chapter, we will describe the role of CD4 T cells in the development of RA and the abnormalities that these lymphocytes show in diseased individuals.

2. Aetiology of rheumatoid arthritis

Although the aetiology of RA remains elusive, genetic and environmental risk factors have been described [16, 17]. MHC-II genes, particularly HLA (human leukocyte antigen) -DRB1 alleles (the so-called shared epitope [18, 19]), constitute the strongest genetic risk factor, accounting for 50% of the genetic contribution to RA [20]. Association with HLA-DRB1 has been established in different populations across the world [21–25], especially in ACPA-positive pathology, and different haplotypes of HLA-DRB1 associate with distinct RA severity and treatment response [26]. Single-nucleotide polymorphisms (SNPs) in other genes have also been linked to RA [16], including genes coding for molecules that regulate T cell activation, which will be discussed below. These genetic associations strongly indicate a decisive role of helper T lymphocytes in the pathology.

The major environmental risk factor is smoking habit, which seems to alter citrullination of mucosal proteins [27]. Genetic and environmental risk factors work together in promoting the disease. For example, smoking habit alters methylation of the HLA-DRB1 region, increasing the chance of developing ACPA-positive RA [28, 29].

Some infectious agents might also be risk factors of RA. For example, there is a positive association between the prevalence of periodontitis and RA [30]. *Porphyromonas gingivalis*, the major causative agent of periodontitis, produces an enzyme that induces aberrant citrullination of host proteins [31]. This generates neoantigens that can then be recognised by the immune system of the host, triggering ACPA production. In addition, it has been shown that ACPA from RA patients cross-react with various autoantigens and microbial and plant-citrullinated proteins [32]. This suggests that environmental factors such as infections and diet may trigger

the production of ACPA in individuals with genetic predisposition. ACPA can then cross-react with self-proteins through molecular mimicry, inducing RA.

3. Pathophysiology of rheumatoid arthritis

A healthy joint (**Figure 1A**, left side) is composed of two adjacent bony ends covered with a layer of cartilage. The space between ends is called articular cavity, which is delimited by the synovial membrane on both sides and contains synovial fluid. The synovial membrane is a thin layer of cells, formed by two types of synoviocytes: type A or macrophage-like synovial cells
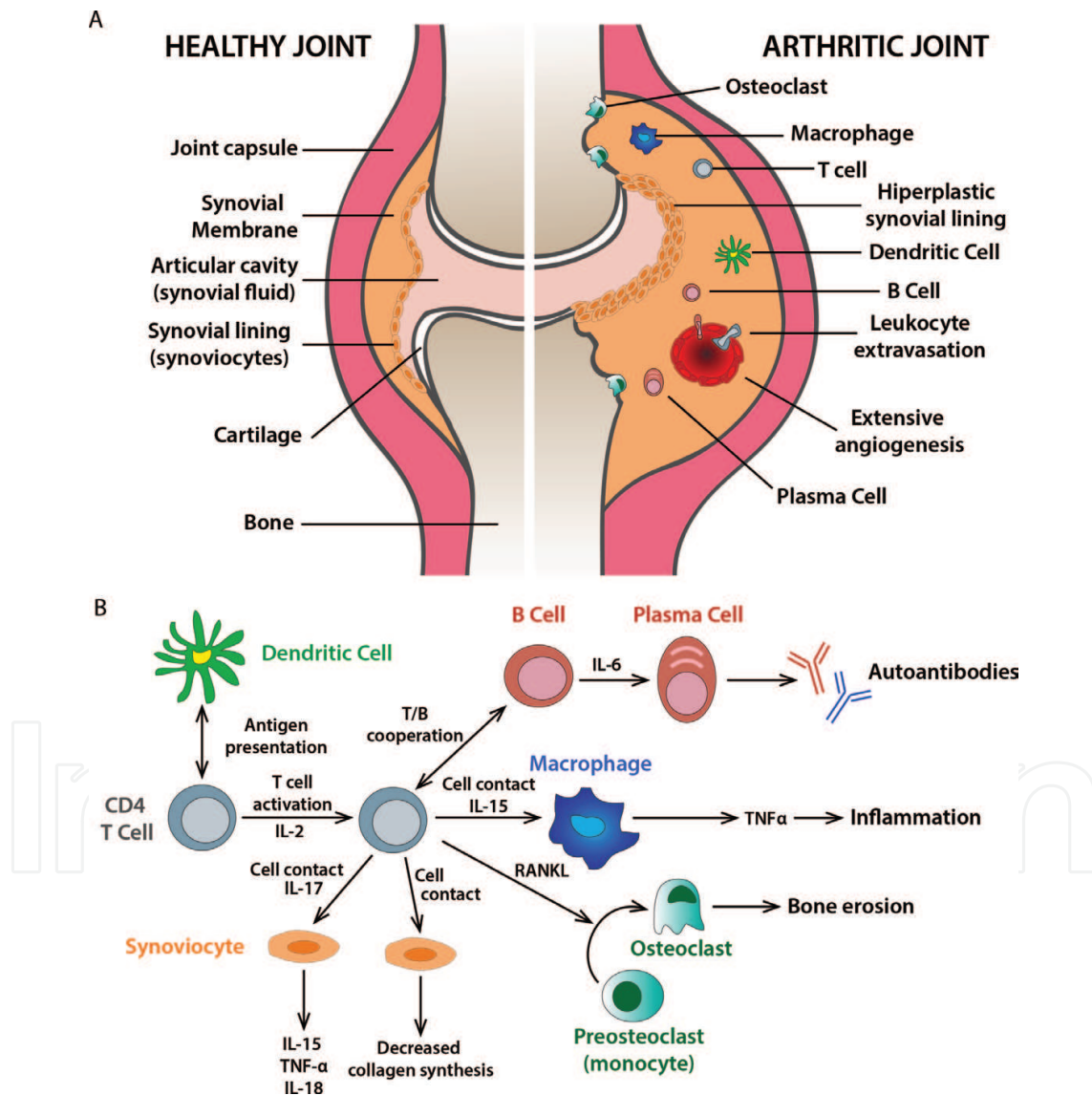
Figure 1. Role of CD4 T cells in rheumatoid synovitis. (**A**) In a healthy synovial joint (left), a thin layer of synoviocytes delimits the joint capsule. By contrast, in RA (right), synoviocytes form an invasive synovial lining and leukocytes infiltrate the synovial membrane. (**B**) Activated CD4 T cells play a central role in inflammatory responses in the synovial membrane, including autoantibody production by plasma cells, secretion of inflammatory cytokines by macrophages and synoviocytes, bone erosion by osteoclasts and inhibition of collagen secretion by synoviocytes.

and type B or fibroblast-like synoviocytes (FLSs). The synovial membrane produces synovial fluid and due to its porous organisation allows diffusion of the nutrients in serum to the avascular cartilage.

The confluence of genetic susceptibility and environmental factors determines the development of an autoimmune response that precedes clinical arthritis. For reasons poorly understood, this autoimmune response exacerbates in the synovium, where leukocytes infiltrate causing synovial membrane inflammation (rheumatoid synovitis) (**Figure 1A**, right side). Synovial infiltrate includes both innate and adaptive immune cells [33, 34] and creates a microenvironment where FLSs acquire an invasive and inflammatory phenotype, leading to hyperplasia of the synovial lining [35, 36]. FLSs secrete matrix metalloproteinases (MMPs) and collagenase, promoting cartilage destruction [37]. Leukocyte infiltration and secretion of pro-inflammatory cytokines favour maturation of pre-osteoclasts to osteoclasts, which leads to bone erosion [38–40]. Cytokines and growth factors released by infiltrated cells, together with the hypoxia resulting from synovial hyperplasia, trigger angiogenesis [41–43], establishing a feedback loop that favours continuous leukocyte infiltration and chronic inflammation.

Inflammation initiated in the synovium gives way to systemic inflammation that alters the function of distant tissues and organs, such as vascular endothelium, adipose tissue, liver and lungs. As a result, ExRA is present in RA patients, such as cardiovascular disease (CVD), anaemia or rheumatoid lung, among others [44].

Although different immune cells infiltrate the inflamed joint, we will focus on CD4 T cells, which, as mentioned above, seem to be central in the pathophysiology of RA by secreting cytokines and by cooperating with synovial cells.

4. Pathogenic role of CD4 T cells in rheumatoid arthritis

4.1. CD4 T cell activation and function in synovitis

CD4 T cells are the most abundant lymphocyte in the synovial infiltrate [45], where they regulate other cell types in the synovium and play a central role in the pathological immune response leading to the joint damage (**Figure 1B**).

4.1.1. CD4 T cell activation by DCs

Dendritic cells (DCs) are key initiators of adaptive immune responses, since they are professional antigen-presenting cells (APCs), able to present to T cell antigenic peptides in the context of the MHC-II. Initially, infiltrated CD4 T cells interact with synovial DCs, resulting in T cell stimulation (**Figure 1B**). Activation of CD4 T cells requires the engagement of the T cell receptor (TCR) by antigen-MHC-II complexes on the surface of the APC. In addition, full T cell activation requires interaction between the molecule CD28 on the T cell and its ligands CD80 and CD86 expressed by APCs, which provides costimulatory signals. Activated CD4 T cells upregulate the expression of the inhibitory molecule cytotoxic T lymphocyte antigen-4 (CTLA-4), which binds CD80 and CD86 with higher affinity

than CD28 [46]. During consecutive contacts with APCs, CTLA-4 will compete with CD28 for CD80/CD86, and binding of CTLA-4 to these ligands will result in inhibition of T cell activation [47]. The importance of APC-mediated T cell costimulation for the progression of RA has been proved by therapy with the CTLA-4-immunoglobulin fusion protein abatacept. This molecule binds to CD80/CD86 on the APC, impeding binding of CD28 and, therefore, blocking T cell costimulation [48]. Treatment with abatacept reduces disease activity and radiographic progression of RA [49, 50].

4.1.2. Cooperation between CD4 T cells and B cells

B cells play a fundamental role in seropositive RA, in which patients develop autoantibodies contributing to inflammation and tissue damage. Autoantibodies are synthesised by plasma cells, which differentiate from B cells after cooperation with CD4 T cells. Upon activation, T cells upregulate the surface expression of CD40 ligand (CD40L or CD154), which interacts with CD40 expressed by B cells. During T/B cooperation, stimulation through CD40 together with IL-6 signalling favours isotype switching, differentiation of B cells into plasma cells and synthesis of antibodies such as ACPA (**Figure 1B**) [51]. CD4 T cells, B cells and DCs found in joints of RA patients range from diffuse infiltrates to follicular structures, forming ectopic germinal centres (EGCs) in some patients [52]. Formation of EGCs favours the formation of high affinity autoantibodies, increasing the severity of the disease [53]. EGCs and B cells seem to be critical for T cell activation in the synovium [54].

4.1.3. Regulation of FLSs by CD4 T cells

As mentioned before, FLSs are an important component of joint architecture. In a healthy joint (**Figure 1A**, left side), FLSs form the synovial lining and produce synovial fluid. FLSs acquire an invasive phenotype in RA, causing hyperplasia of the synovial lining (**Figure 1A**, right side). This hyperplasia originates a hypoxic environment where angiogenesis is activated, favouring perpetuation of inflammation. In addition, RA FLSs secrete high amounts of proteases, which trigger cartilage destruction, and pro-inflammatory cytokines.

Antigen-experienced CD4 T cells affect the function of FLSs by direct cell-cell interaction. For example, CD4 T cells induce the production of the pro-inflammatory cytokines IL-15, TNF-α and IL-18 by FLSs (**Figure 1B**). This is dependent on CD40L-CD40 engagement as demonstrated by a blocking agent [55]. Collagen synthesis by FLSs is also decreased by CD4 T cells, a process mediated, at least in part, by T cell membrane-associated IFN-γ, TNF-α and IL-1α [56].

4.1.4. Regulation of macrophages/monocytes by CD4 T cells

Macrophages infiltrate the RA joint, where they interact with synovial cells and produce the pro-inflammatory cytokine TNF-α. CD4 T cells regulate macrophages in the synovium, as shown by the finding that freshly isolated synovial T cells can induce the expression of the pro-inflammatory cytokine TNF-α by macrophages in an IL-15-dependent manner (**Figure 1B**) [57]. Resembling the behaviour of T cells in RA patients, T cells of healthy donors stimulated with an inflammatory cytokine cocktail can induce the production of TNF-α by

resting monocytes [58]. It should be noted that TNF-α production by myeloid cells is also induced by IL-15-stimulated NK cells [59]. Due to the central role of TNF-α in the progression of RA, as demonstrated by the succeeded neutralising therapy [60], it will be needed to further investigate this complex regulation of immune cells in the inflamed joint.

Monocytes are the progenitors of osteoclasts, which constitute the only cell type that is able to degrade bone. In health, bone resorption by osteoclasts and bone generation by osteoblasts are tightly regulated to maintain skeletal integrity and homeostasis. In RA, osteoclast activity in the joint is increased, resulting in an unbalanced bone erosion. Synovial CD4 T cells from RA patients, as well as activated peripheral blood T cells from healthy donors, express receptor activator of nuclear factor κB ligand (RANKL), which engages RANK expressed on monocytes, inducing their differentiation to osteoclasts [61, 62] and, consequently, triggering bone erosion (**Figure 1B**).

4.1.5. Role of IL-17 secretion by T cells

Synovial CD4 T cells produce pro-inflammatory cytokines themselves (**Table 1**). Among these, IL-17 expression is increased in the synovial tissue of RA patients [63], its levels correlate with disease activity [64] and it has a predominant role in rheumatoid pathology [65]. This cytokine is produced by Th17 cells that are critical drivers of synovitis [66]. In the synovium, IL-17 stimulates the production of pro-inflammatory cytokines by rheumatoid synovial cells [67, 68], triggers osteoclastogenesis [69] and impairs cartilage repair [70]. Methotrexate, a first-line conventional therapeutic agent in RA, attenuates IL-17 production by peripheral blood mononuclear cells in vitro [71], supporting the pathogenic role of this cytokine.

Interestingly, the balance between Th17 and regulatory T cells (Treg), which exert anti-inflammatory functions, is shifted towards the Th17 subset in RA [72]. The first hypothesis explaining the excessive Th17 response in RA is that it might be an enhanced Th17 differentiation due to the inflammatory environment. Th17 cells differentiate in the presence of IL-1β, IL-6 and IL-23 [73], which are secreted by activated macrophages and dendritic cells in inflammatory conditions [74]. Supporting this hypothesis, both IL-23 and IL-6 levels are increased in patients with RA [75, 76]. IL-23 levels correlate with the activity of early arthritis [77]. A second hypothesis would be that intrinsic alterations in naïve CD4 T cells might prone Th17 rather than Treg differentiation. Supporting this hypothesis, naïve RA T cells overexpress glucose-6-phosphate dehydrogenase (G6PD), which causes insufficient activation of ataxia telangiectasia mutated (ATM), leading to biased differentiation of CD4 T cells towards Th17 and Th1 subsets (**Table 2**) [78].

4.2. Abnormalities in CD4 T cell activation and signalling

As mentioned in the previous sections, CD4 T cell activation in the synovium is a key event in RA pathology. CD4 T cell activation is initiated by interaction of the TCR with the antigen-MHC-II expressed on the surface of an APC. Engagement of TCR/MHC-II-antigen complex triggers the activation of intracellular signalling networks in which phosphorylation plays a decisive role. The kinases Lck and ZAP70 are rapidly activated after TCR stimulation and activate downstream effectors such as extracellular signal-regulated kinase (ERK) to induce

Cytokine	Pathogenic role
TNF-α	• Activates leukocytes, synovial fibroblasts, endothelial cells and osteoclasts • Induces production of inflammatory cytokines • Enhances metalloproteinase expression • Suppresses Treg cells
IFN-γ	• Increases antigen presentation • Activates macrophages • Increases chemokine secretion
IL-1	• Activates leukocytes, synovial fibroblasts, endothelial cells and osteoclasts • Induces production of matrix proteinases
IL-6	• Activates leukocytes and osteoclasts • Stimulates antibody production
IL-17	• Induces production of inflammatory cytokines • Activates innate immune cells • Increases osteoclastogenesis • Stimulates neutrophil recruitment
IL-21	• Activates Th17 and B cells

Table 1. Pathogenic role of cytokines secreted by CD4 T cells in the RA synovium.

gene expression and cell proliferation. In physiologic conditions, signalling downstream the TCR is tightly regulated by proteins such as phosphatases. In T cell-mediated autoimmune pathologies, such as RA, intracellular signalling is deregulated, leading to alterations in T cell responses.

Another physiological mechanism regulating T cell responses and preventing autoimmunity is the elimination of self-reactive T cells. This mechanism is called tolerance and occurs both on immature T cells in the thymus (central tolerance) and on mature circulating T cells (peripheral tolerance). In RA, activation of CD4 T cells by self-antigens seems to be permitted by losing peripheral or central tolerance and promoted by enhanced sensitivity to self-antigens due to alterations in signalling networks integrating extracellular stimuli.

Several observations indicate that peripheral blood, and not only synovial-infiltrating T cells, show hyper-activation in RA patients [79, 80]. An aberrant function or expression of signalling molecules, some of them regulating T cell responses, has been found in CD4 T cells of RA patients (**Table 2**) and will be discussed below.

Protein	Alteration	Consequence in CD4 T cells	Reference(s)
G6PD	Overexpression	• Insufficient ATM activation • Hyperproliferation • Increased Th1/Th17 differentiation	[78]
LYP (rs2476601 SNP)	Gain of function mutation	• T cell hyporesponsiveness	[88–92]
TC-PTP (rs1893217(C) SNP)	Reduced expression	• Decreased STAT5 phosphorylation • Decreased FOXP3 expression upon activation	[95, 96]
CDC25B	Reduced expression	Not reported	[99]
DUSP7	Reduced expression	Not reported	[99]
B-RAF K-RAS	Overexpression	• Increased ERK phosphorylation and signalling • Autoreactive response to citrullinated peptides	[101]
PD-1	Reduced expression	Not reported	[91–95]
Telomerase	Insufficient induction	Susceptibility to apoptosis	[12]
MRE11A	Reduced expression	• Telomeric damage • Senescence	[11]

G6PD, glucose-6-phosphate dehydrogenase; ATM, ataxia telangiectasia mutated; LYP, lymphoid-specific tyrosine phosphatase; TC-PTP, T cell protein tyrosine phosphatase; STAT5, signal transducer and activator of transcription 5; FOXP3, forkhead box P3; CDC25B, cell division cycle 25 B; DUSP7, dual-specificity phosphatase 7; ERK, extracellular signal-regulated kinase; PD-1, programmed death 1; MRE11A, meiotic recombination 11 homolog A

Table 2. Alterations in gen/protein expression or activity found in CD4 T cells from RA patients and their phenotype.

4.2.1. PD-1

Programmed death-1 (PD-1) receptor is inducibly expressed on CD4 T cells upon activation through the TCR [81]. Upon binding to its ligands during TCR stimulation, PD-1 delivers inhibitory signals that suppress T cell activation and proliferation and impair T cell survival [82]. A set of SNPs in the gene coding for PD-1 are linked to RA [83–85], and PD-1 expression is decreased in T cells from RA patients [86]. This reduced expression would lead to a defect in peripheral tolerance, favouring autoimmunity.

4.2.2. LYP

The lymphoid-specific tyrosine phosphatase (LYP) is encoded by the gene *PTPN22*. This protein is exclusively expressed in cells of the immune system and in T cells negatively regulates TCR signalling by inactivating the kinases Lck and ZAP70 [87]. Therefore, LYP is an important inhibitor of signalling downstream the TCR. The SNP rs2476601 in *PTPN22* is associated with RA [88, 89]. The pathological function of this SNP, which results in the LYP mutant R620W, remains controversial. Various reports show that the LYP R620W variant is more effective in

downregulating TCR signalling than the LYP WT [90, 91]. In this situation, LYP R620W would trigger autoimmunity because it would suppress TCR signalling of autoreactive T cells during negative selection in the thymus, promoting their survival and compromising central tolerance [92]. Molecular mechanisms leading to autoimmunity in the presence of this polymorphism should be further studied.

4.2.3. TC-PTP

The T cell-phosphotyrosine phosphatase (TC-PTP) is encoded by the gene *PTPN2*. This tyrosine phosphatase negatively regulates TCR and JAK-STAT signalling, being an inhibitor of T cell activation [93, 94]. The SNP rs1893217(C) in *PTPN2* is associated with juvenile idiopathic arthritis and results in decreased gene expression [95]. Strikingly, decreased phosphorylation of STAT5 and reduced FOXP3 expression are found in cells carrying this mutation [96]. Because FOXP3 is the master regulator of Treg differentiation [97], this SNP might cause abnormalities in Treg functions, resulting in increased inflammation. The mechanism for this phenotype should be investigated.

4.2.4. CDC25B

The dual-specificity phosphatase cell division cycle 25 B (CDC25B) positively regulates cell proliferation by promoting G2/M transition [98]. Recently, our group has found a reduced expression of this phosphatase in CD4 T cells of patients diagnosed with early arthritis [99]. Importantly, altered CDC25B levels associate to the activity of the disease. Whether this alteration causes or is a consequence of the inflammatory environment characteristic of RA, and its effect in T cell responses will need further investigation.

4.2.5. Regulators of ERK signalling

As mentioned before, ERK is a key effector molecule downstream TCR activation. Hence, defective regulation of ERK phosphorylation levels could lead to aberrant T cell responses. The expression of some ERK regulator is altered in T cells of RA patients.

The dual-specificity phosphatase 7 (DUSP7) negatively regulates ERK phosphorylation and activity [100]. Although its role in T cells has not been addressed, it is conceivable that DUSP7 could be a negative regulator of MAPK signalling in T cells being activated. CD4 T cells of patients with seropositive early arthritis have reduced expression of DUSP7 [99]. The fact that defective expression is restricted to seropositive patients could indicate a role of this phosphatase in T/B cooperation. Further investigation is needed to determine the functional significance of DUSP7 in T cells.

The GTPase K-RAS and the kinase B-RAF are positive regulators of ERK signalling upon TCR stimulation. A higher TCR-induced ERK phosphorylation results in a lower T cell activation threshold, contributing to autoimmunity. K-RAS and B-RAF are overexpressed in T cells of RA patients [101]. Interestingly, overexpression of B-RAF and K-RAS increases the activation of CD4 T cells of healthy donors by a citrullinated vimentin peptide. This finding provides support to the notion that higher CD4 sensitivity could cause loss of peripheral tolerance in RA patients.

4.3. Abnormalities in CD4 T cell repertoire and aging

The ability of the adaptive immune system to respond to the large diversity of pathogens found throughout life depends on the generation of a wide TCR repertoire. This repertoire is generated in the thymus, where the V, D and J segments of the TCR rearrange randomly. Newly generated naive T cells migrate from the thymus to the periphery to exert their functions. The thymic output, however, declines throughout life. In the elderly the thymus no longer functions as a source of new naïve T cells, which have to be produced by replication of mature peripheral T cells, a process called homeostatic proliferation [102]. The expansion of peripheral T cell clones generates a contraction in T cell repertoire and induces a phenotype of replicative stress that is characteristic of aged people [103]. Clone expansion of peripheral cells might favour an increased presence of autoreactive clones. Consistent with this idea, autoimmune signs such as autoantibody production are higher in elderly individuals [104].

Repertoire contraction and clonally expanded populations in the CD4 compartment have been reported in RA [105]. Clonal expansion was initially interpreted as a consequence of specific responses to synovial self-antigens, but this hypothesis is unlikely. Contraction in CD4 T cell diversity is not limited to the memory compartment, but involves also naïve T cells [106]. This seems to be due to an accelerated aging of the immune system in RA patients, in which the thymus function is lost earlier than in healthy people [107].

A hallmark of immune aging is the accumulation of end-differentiated effector CD4 T cells that lack expression of the costimulatory receptor CD28 [108]. Indeed, the frequency of CD4+ CD28− lymphocytes is higher in RA patients [109, 110]. These cells are producers of IFN-γ, display cytotoxic functions and are autoreactive [109, 111, 112]. Such phenotype could be mediated, at least in part, by increased expression of the NK cell-activating receptor NKG2D. Ligands of NKG2D are highly expressed in inflamed synovium [113].

Another hallmark of cellular aging is telomere shortening [114], and lymphocytes from RA patients show premature telomeric loss [115]. In naïve CD4 T cells, this is due to insufficient upregulation of telomerase activity (**Table 2**), which in addition promotes apoptosis in these cells [12]. Excessive loss of naive T cells will further stimulate homeostatic proliferation of effector T cells, providing a positive feedback loop of replicative stress.

Recently, another alteration in DNA repair machinery was found in CD4 T cells from RA patients [11]. The expression of repair nuclease MRE11A is decreased in these cells, leading to telomeric damage and upregulated senescence markers (**Table 2**).

4.4. CD4 T cells in extra-articular disease

Although the main site of inflammation in RA is the synovium, pro-inflammatory cytokines and activated cells are released to the bloodstream, leading to systemic inflammation. This inflammatory state has multiple ExRA on distant organs, such as skin, lungs, heart, blood or bone [116]. Smoking habit and autoantibodies predispose to severe ExRA [117]. Several systemic

pathologies are frequent in RA patients, such as systemic vasculitis, interstitial lung disease and pericarditis, which is the most common cardiac complication [116]. We focus here on CVD.

Chronic inflammation generates a pro-atherogenic environment in RA. Indeed, RA patients have increased risk of cardiovascular death [118] and higher incidence of atherosclerotic heart disease [119]. Atherosclerosis is an inflammatory process in which the plaque, constituted by lipid accumulation on arterial walls, causes endothelial injury and activation. This promotes the recruitment of leukocytes, which culminates in the disruption of the plaque and thrombosis. Vascular inflammation in atherosclerosis and synovial inflammation in RA share features of immune activation, including accumulation of inflammatory macrophages and T cells, production of inflammatory cytokines and degradation of the extracellular matrix. High levels of soluble factors such as C-reactive protein, TNF-α and IL-6 are associated with coronary artery disease [120–122]. These cytokines are also elevated in chronic inflammation, which renders lipoproteins more atherogenic, reduces the repair of injured endothelium and upregulates the expression of endothelial adhesion molecules, which enhance leukocyte recruitment [123]. Consistent with a role of systemic inflammation in atherosclerosis, RA therapies based on methotrexate and TNF-α antagonists decrease CVD rates [124, 125].

As mentioned before, the CD4+CD28− T cell subset is expanded in RA [109, 110]. This T cell subset is also expanded in patients with unstable angina (UA) [126], a pathology in which the atheroma plaque is disrupted causing thrombosis. The percentage of CD4+CD28− cells correlates with recurrence of UA, pointing to a direct role of these cells in the progression of the pathology [127]. In addition, expanded CD4+ CD28− found in the atherosclerotic lesion includes large monoclonal populations, suggesting that these cells can recognise antigens in the atheroma plaque [128]. Consistently, RA patients with expansion of circulating CD4+CD28− cells show preclinical atherosclerotic changes, including endothelial dysfunction [129]. The implication of CD4+CD28− cells in atherosclerosis is further supported by anti-TNF therapy, which normalises CD28 expression [130] and decreases CVD rates [125].

5. Conclusion

RA is a chronic inflammatory disease characterised by synovitis and systemic features, such as exacerbated atherosclerosis. CD4 T cells are key mediators of tissue damage, both in the joint and in extra-articular lesions, through a variety of mechanisms. Certain alleles of the MHC-II as well as different alterations of signalling molecules and checkpoints for activation seem to favour self-antigen recognition, activation and break of tolerance. Besides, abnormalities found in CD4 T cell repertoire and phenotype in patients with RA strongly suggest that in these patients there is an accelerated aging of the immune system that leads to oligoclonality and senescence of T cells, making these lymphocytes autoreactive. Understanding the mechanisms underlying these systemic alterations will be essential for the development of more effective therapies for RA treatment.

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