Review

Rampant infections of bone marrow stem cell niches as triggers for spondyloarthropathies and rheumatoid arthritis

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ABSTRACT

Tropheryma Whipplei can induce rheumatism mimicking SpA or RA, but even more rampant bacterial/viral infections in epiphyseal bones could also contribute to the onset of RA and SpA. Indeed, as bone marrow stem cell niches are enriched in Tregs and myeloid derived suppressor cells, these areas are favourable for the persistence of quiescent viruses and/or dormant bacteria. This review focuses on the possibility that such silent infections of bone marrow stem cell niches might contribute to the pathogenesis of SpA and RA, at least during their onset. Some infections can affect the bone marrow mesenchymal stem cells, which can transmit these pathogens to their progeny. Transient but repeated revivals of viruses or dormant bacteria could promote the conversion of marrow regulatory T cells into effector phenotypes, leading to autoimmunity in the epiphyseal bone marrow, entheses and adjacent synovium. This scenario would also fit the flares of rheumatic disorders and explain why some joints or entheses can be severely involved whereas their neighbours remain intact. The efficiency of anti-TNF drugs does not rule out a role of persistent infections in SpA and RA. These drugs do not affect chlamydial clearance, or the reactivation of latent Salmonella enterica serovar Typhimurium in mice or Epstein-Barr virus in humans. Anti-TNF might even prevent, rather than foster, the revival of dormant bacteria and viruses in marrow stem cell niches. Indeed, anti-TNF enhance the maturation of the immunosuppressive immature myeloid cells around stem cells into dendritic cells and macrophages, thus restoring immune responses in these areas.

Rampant infections could help to induce and sustain abnormal immune responses in RA and SpA

Rheumatoid arthritis (RA) is considered to be an auto-immune disorder. The recent demonstration that several auto-antibodies are also present in spondyloarthropathies (SpA) (1) (including antibodies with specificity for a CLass II-associated Invariant chain Peptide, called anti-CLIP = anti-CD74 antibodies (2)) supports the hypothesis that SpA could also be driven by auto-immune processes. In any case, as both conditions are strikingly improved by various immunosuppressive drugs, including anti-TNF agents, their pathogenesis is obviously driven by over-responses of the innate and/or adaptive immune system.

However, the concept of the "infectome" (sum of an individual's exposures to infectious agents within his/her lifetime) was recently introduced to emphasise the need to not forget the contribution of infectious factors to the development of auto-immune disorders (3).

This scenario might be relevant to SpA (4) and RA (5), since several lines of evidence suggest that rampant infections could contribute to their pathogenesis.

In animal models, many studies have shown that microbial infections can induce and/or exacerbate the symptoms of experimental arthritis through numerous mechanisms (5): for instance, SpA does not occur in HLA-B27 transgenic rats bred under sterile conditions (4). In humans, DNA from various bacterial species could be found in up to 75% of synovial tissues from patients with reactive or undifferentiated arthritis (6), while more than one species could be detected in 35% of PCR-positive patients (7). In children with juvenile arthritis, although blood stream infection remains rare, its incidence is 3-fold higher than in the general population (8).

Numerous pathogens could indeed cooperate in a single patient to disturb the immune response, in the joints but also in other locations like the bone marrow

and mucosal lymph nodes, until the onset of arthritis. This combination of pathogens might differ from one person to another, explaining why the search for a single infection antedating RA or SpA in all patients with one of these disorders has failed. For instance, more than 30 infectious agents (*Chlamydiae*, *Yersiniae*, etc…) can trigger the onset of reactive arthritis (9), and the same patient can experience flares of reactive arthritis following infections by different bacteria. Moreover, some of these infections can remain silent for long periods and only be diagnosed several years after the onset of chronic rheumatism. Whipple's disease is a very good example of such a possibility (10). However, many other bacteria from the gut, lungs or tissue specific microbiomes could also behave as even more silent but pathogenic pathobionts, due to virulence factors or defects in the host's innate immunity, as illustrated by the contribution of *Porphyromonas gingivalis* to periodontitis (11).

Although elevated serum anti-flagellin antibodies can be found in some cases of persistent SpA (12) and elevated anti-viral antibodies in the majority of chronic RA patients (13), whether rampant infections also sustain most cases of SpA or RA after their onset is much more open to debate. The three main objections to a leading role of bacteria and/or viruses in maintenance of the autoimmune processes of SpA and RA long after their onset are (besides the banality of PCR positivity for many pathogens in both arthritic and normal synovium): 1-the observation, in animal models of RA and SpA induced by immunisation against joint components, that autoimmunity can persist without concurrent infections, or the need to repeat the immunisation with the same joint autoantigen(s) used during the boosting phase; 2-the usual failure of antibiotics to stop, or even reduce, the activity of RA or SpA; 3-the marked improvement often observed following anti-TNF therapy (in RA and SpA), or rituximab (RTX) (in RA), which are usually considered to be immunosuppressive drugs, with infections being the main side effects.

The first argument cannot be rejected, since most human autoimmune diseases last for several years, or a lifetime, once initiated. However, most of the methods used to induce autoimmunity in mice, including boosting the immune response with adjuvants, are quite different from the mechanisms driving autoimmunity in humans. One exception could be the model of Tsumiyama *et al.*, who showed that repeated stimulation with enterotoxin every 5 days (up to 24 times), without adjuvant, was sufficient to induce rheumatoid factor, anti-galactose and anti-Sm, together with features of arthritis or clinical lupus, in Balb-c mice (14-15). Repeated revivals of rampant infections in their niches (like bone marrow stem cells) could likewise drive lasting autoimmunity in humans (16), especially as chronic subversion of Tregs in animal models of RA leads to their conversion into Th17 cells with an effector phenotype (17). Studies of the role of HLA-B27 in the pathogenesis of SpA revealed an enhanced intracellular replication of bacteria like *Salmonella enteritidis* in human monocytic cells expressing HLA-B27 (18), possibly favoured by their defective presentation with a reverse interferon signature by HLA-B27 positive dendritic cells (19). Accordingly, persistent dormant infections with transient revivals cannot be ruled out as cofactors sustaining SpA or RA, particularly as flares of these disorders are frequent. These flares can indeed be better explained by the transient awakening of infectious agents than by the stochastic fluctuations of an autoimmune process.

The two other objections also deserve to be re-examined. Firstly, the failure of antibiotics does not exclude a role of dormant or defective bacteria or viruses in the pathogenesis of SpA (and perhaps some types of RA). Thus, quiescent bacteria, which do not replicate, are not sensitive to the usual antibiotics and their persistence can even be favoured by inappropriate administration of antibiotics (20). In an animal model of complicated salmonellosis, despite high-dose ciprofloxacin therapy, approximately 10-20% of the bacteria (displaying a very slow growth rate) remained viable in the cecum draining lymph nodes, gut tissue and spleen (21). The involvement of dormant bacteria in the pathogenesis of SpA would be consistent with the observation that certain forms of cell stress such as molecule misfolding, a feature of HLA-B27, promote the entry of bacteria into a state of dormancy, which induces the low-level release by the host cells of cytokines such as TNF (20).

Secondly, although anti-TNF and rituximab (RTX) undoubtedly slightly increase the risk of overt infections, anti-TNF could also, paradoxically, favour the control of some dormant bacteria and viruses in stem cell niches (22). This property could be one of the mechanisms whereby anti-TNF induce dramatic and lasting improvement in some (but not all) RA and SpA patients. The same might hold true for the better control of RA following repeated cures with RTX, since RTX can reduce the load of viruses like Epstein-Barr virus (23).

This review focuses on the possibility that silent infections of bone marrow stem cell niches contribute to the pathogenesis of SpA and RA, at least during their onset, their revival being prevented rather than fostered by anti-TNF through the maturation of immature myeloid cells surrounding these niches.

Many viruses and dormant bacteria can infect stem cells and use them as reservoirs

If dormant bacteria or viruses help to sustain SpA or RA, they might persist in long living cells like memory cells in lymph nodes, or stem cell niches (either haematopoietic or mesenchymal) in bone marrow. Bone marrow stem cells can indeed transmit silent infections to their progeny, leading to further traffic in joints or entheses and arthritis (24). Other mesenchymal stem cells are also present in the joint or epiphyseal bone marrow, like stem cells arising from adipose tissue (25). Stem cell niches could also be the most advantageous place for some bacteria or viruses for another reason: they exert an immunoregulatory role, which prevents the immune system from targeting them (26), and are highly enriched in Tregs which might be manipulated by pathogens to help them persist (27).

This immune privilege makes this small area more vulnerable to lasting

infections. For instance, mature neutrophils derived from normal human adult bone marrow CD34+ cells have limited bactericidal ability (28), while the same holds true for the surrounding macrophages which are more susceptible to intracellular pathogens (29).

The use of stem cells as reservoirs by some viruses or bacteria has undesirable consequences for the host, in the case of both haematopoietic stem cells which play a pivotal role in directing the immune response from the bone marrow (30), and mesenchymal stem cells. In a transgenic mouse model of SpA, the development of arthritis required TNF receptor I (TNFRI) expression in mesenchymal stem cells, which is also known to be a sufficient target of TNF for the development of Crohn's-like inflammatory bowel disease (31). As silent intracellular infection can also induce the expression of TNF, the existence of such phenomena in the epiphyseal stem cells of patients with arthritis/enthesitis would explain, better than widespread breakdown of tolerance to some auto-antigens, why in a single patient, some joints or entheses can be seriously involved for decades whereas their neighbours remain intact during the whole period.

Viruses can infect stem cells and their niches (Table I)

Human parvovirus B19 infection is restricted to the erythroid progenitor cells of human bone marrow (32) and mesenchymal stromal cells (33). Haematopoietic stem/precursor cells can act as HIV reservoirs (34-35). Hepatitis B virus (HBV) can also replicate in human bone marrow mesenchymal stem cells (36) and the infected cells generate defective T cells (37). Hepatitis C virus (38) and HHV8 (39)similarly infect haematopoietic progenitors. Herpes virus 1 (40) and cytomegalovirus (CMV) (41-42) have been found in human mesenchymal stromal cells. The stromal cells infected by CMV lose their immunosuppressive capacity and are no longer able to restrict microbial growth (41). Teno-Torque virus can infect haematopoietic stem cells and transplantation of these cells has led to autoimmunity in the recipients (43). Human T cell leukaemia virus type I (HTLV-1) can hide in bone marrow stromal cells (44), and bone marrow-derived cells are responsible for the development of autoimmune arthritis in HTLV-1 transgenic mice (45). In humans, patients infected with HTLV-1 can likewise develop arthritis, periodontal disease, uveitis, sicca syndrome or neurological defects (46). HLTV1-1 can also induce adult T-cell leukaemia/lymphoma, which is a malignancy of regulatory T cells (Tregs)/TH2 cells with a high frequency of expression of CD25/CCR4 and FoxP3 in about half of the cells (47).

Table I. Some viruses can infect stem cells.

Human parvovirus B19 (erythroid progenitor cells (32), stromal cells (33))
HIV (haematopoietic stem/precursor cells) (34-35)
Hepatitis B virus (HBV) (bone marrow mesenchymal stem cells) (36-37)
Hepatitis C virus (38) and HHV8 (haematopoietic progenitors) (39)
Herpes virus 1 (40) and cytomegalovirus (mesenchymal stromal cells) (41-42)
Teno-Torque virus (haematopoietic stem cells) (43)
HTLV-1 (bone marrow stromal cells) (44)

Table II. Some (dormant) bacteria can infect stem cells.

- Mycobacterium tuberculosis (54-55)
- Leprosy bacilli (reprogrammation of adult Schwann cells to stem cell-like cells) (60)
- Staphylococcus aureus (mesenchymal cells) (56)
- Mycoplasma (stem cells) (58)
- Chlamydia trachomatis (mesenchymal stem cells) (59)
- Several enteric bacteria (62, 66) promote the trans-differentiation of epithelial cells into a mesenchymal phenotype (64) and force the infected cells to secrete TNF (61)

In RA, EBV was detected in the bone marrow in 15/35 patients and parvoviruses in 12/35 (4 bone marrows being infected by both viruses) (48). These two viruses have long been suspected to contribute to the pathogenesis of RA (49). Moreover, recent studies confirmed that in RA patients, EBV infection of the bone marrow transformed CD25+ B cells into antibody-secreting cells (50), whereas in healthy individuals seropositive for herpes viruses, viral DNA could not be detected in mesenchymal stem cells (51). Whether the development of RA (52) and other rheumatic diseases following stem cell transplantation (53) might be explained by the grafting of infected stem cells remains to be determined, but the simplicity of this hypothesis makes it attractive.

Some bacteria can infect stem cells and their progeny, including immature myeloid cells (Table II)

Mycobacterium tuberculosis can persist in human haematopoietic stem cells and bone marrow mesenchymal stem cells *in vitro*, and *in vivo* in mice (54-55). Some human mesenchymal cells are also able to internalise *Staphylococcus aureus in vitro* and the infected cells secrete more IL-6 and TNF (56). The *Mycoplasma* contamination rate in stem cell cultures (about 5%) is a limitation for cell therapy (57). *Mycoplasma* contamination of murine embryonic stem cells affects the cell parameters and chimeric progeny. Indeed, 40% of the chimeras produced from embryonic stem cells infected with *Mycoplasma* species (*Mycoplasma hominis*, *fermentans* and *orale*) suffered from osteoarthropathia and displayed increased levels of anti-DNA antibodies ($p<0.05$) and rheumatoid factor ($p<0.01$) (58). *Chlamydia trachomatis* can also infect human mesenchymal stem cells and persist in them by evading the host immunity through inhibition of NO production (59). It has further been observed that reprogramming of adult Schwann cells to stem cell-like cells by leprosy bacilli promotes dissemination of this infection (60).

It has recently been shown that several of the bacteria known to trigger reactive arthritis can persist, at least *in vitro*, in

human mesenchymal or haematopoietic cells (59, 61). This is in line with the observation that enteric pathogens can exploit the innate plasticity of epithelial cells to promote their trans-differentiation into a mesenchymal phenotype in a process called epithelial-to-mesenchymal transition (EMT) (62), which contributes to oncogenesis in some digestive cancers (63). This epithelial-to-mesenchymal transition is enhanced by flagellin and TGF-beta-1 (64). The intracellular bacteria force the stem cells to secrete various cytokines, including TNF (61), whereas non-infected reactive bone marrow stromal cells usually attenuate systemic inflammation by secreting soluble TNF receptor-1 (65). This has been reported in murine embryonic cells, which are susceptible to invasion by *Salmonella enterica* serovar *Typhimurium* and *Shigella flexneri* (66), and in B cell precursors in murine bone marrow (67). The ability of *Pseudomonas aeruginosa* to infect mouse embryonic stem cells (mESC) has also been demonstrated *in vitro* and depends on a type III secretion system (T3SS), which allows Gram negative pathogens to inject virulent proteins directly into the eukaryotic cell cytoplasm (68). A similar type III secretion system is used by pathogenic *Salmonella enterica* species (69). It has been observed in animal models of reactive arthritis that *Salmonella* with a defective T3SS could induce colitis but not arthritis. Conversely, upon infection by *Salmonella enterica* with an effective T3SS, synovitis appeared soon after colitis and was accompanied by a significant increase in joint tumour necrosis factor alpha (TNF-α) and expression of IL-17 in inguinal and popliteal lymph nodes (69).

Rituximab can clear EBV from blood and this clearance correlates with the improvement observed in RA patients

Rituximab (RTX) can clear EBV from the blood of patients treated for lymphoproliferative disorders: in a study of 17 patients, after three cycles of RTX-based treatment, only 1/17 was still positive for EBV (70). RTX can also cure atypical EBV infection with deceptively negative serology (71). An ancillary study performed within a trial of RTX in new onset type 1 diabetes showed no reactivation of EBV in 57 patients during the 78 weeks following 4 weekly doses of RTX (N=57), whereas EBV could be detected in 6/30 patients from the placebo group (real-time DNA PCR) (72). The same has been observed in RA (73), while in a prospective study the decrease in the DAS-28 in 35 RA patients treated with RTX was significantly better in the 18 patients comprising the EBV-positive group, as compared to the parvovirus-positive (p=0.002) and virus-negative groups (p=0.04). Moreover, most of the EBV-negative patients who responded to RTX (75%) required retreatment within the following 11 months, as compared to only 8% of the responding EBV-positive patients (48). This suggests that EBV-infected cells might indeed contribute to the pathogenesis of RA, although this study did not indicate which subset of infected cells might play the leading role (mature B cells, early B cells or stem cells). Some authors have put forward the hypothesis that the contribution of EBV to RA, lupus and multiple sclerosis could be indirect, since EBV can also activate human endogenous retroviruses (HERV) (74).

Anti-TNF drugs could prevent the revival of dormant bacteria or viruses within stem cell niches

As the main side-effect of anti-TNF drugs is a slightly increased susceptibility to infections, especially to some intracellular pathogens like *Mycobacterium tuberculosis,* most physicians are convinced that anti-TNF agents hamper the control of all intracellular pathogens. However, it should be recalled that in patients with severe sepsis, immunotherapy with anti-TNF-alpha monoclonal antibodies also reduces the overall mortality, as concluded in a recent meta-analysis, while in patients with shock or high levels of IL-6 (>1000 pg/mL), anti-TNF-alpha therapy even improves the survival (75). Similarly, anti-TNF drugs might sometimes allow a better control of some latent intracellular infections.

Firstly, in mice and guinea pigs, anti-TNF therapy has been shown to not significantly affect chlamydial clearance, which occurs quite independently of TNF-alpha (76). This is not so surprising since human monocytes infected with *Chlamydia trachomatis* do not secrete TNF-alpha, but high levels of IL-1, IL-6, IL-8 and IL-10, whereas infected monocyte-derived dendritic cells secrete TNF-alpha, but no IL-1 or IL-10 (77). It has also been shown that treatment with anti-TNF-alpha does not induce the reactivation of latent *Salmonella enterica serovar Typhimurium* infection in C3H/HeN mice (78). Accordingly, anti-TNF might have neutral effects on latent infection of some human cells by these bacteria. This would be in line with the favourable outcome of most patients with reactive arthritis treated with anti-TNF drugs (79). Two outstanding exceptions could be Whipple's disease, which can flare following an anti-TNF trial (and hence be diagnosed several years after the onset of rheumatism) (10), and *Mycobacterium tuberculosis* (80). However, even in the case of *Mycobacterium tuberculosis*, some deletion mutants with compromised ability to mobilise the stored triglycerides in infected cells are unable to emerge from dormancy upon treatment with anti-TNF-α mAbs (80). This shows that the relationships between intracellular bacteria and dormant intracellular pathogens are much more complex and subtle than is generally thought. The same holds true for viruses: two studies showed that neither MTX nor anti-TNF modified the EBV load in patients with rheumatoid arthritis (23, 81). Thus, a lack of revival of infections following anti-TNF therapy does not rule out the possibility of rampant latent infections, with either viruses or intracellular bacteria. Anti-TNF drugs might even prevent the reactivation of some infections in certain areas like stem cell niches.

Although contra-intuitive at first sight, one of the many roles of TNF-alpha is indeed to enhance the suppressive activity of immature myeloid cells during chronic inflammation (22). Even if the results of some experiments are controversial (indications on timing and the duration of TNF-alpha expression are

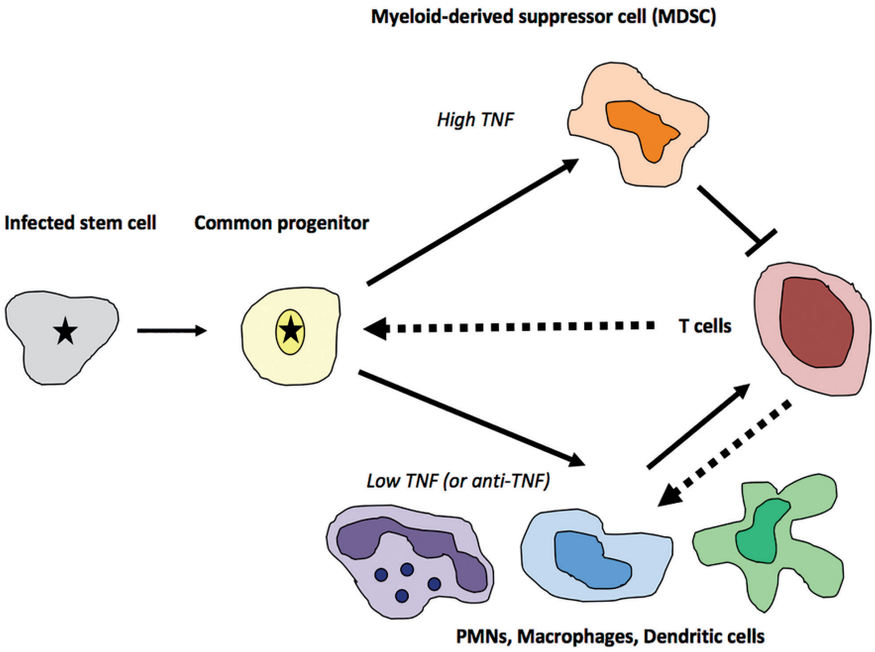

Fig. 1. High TNF levels around stem cells (usually sufficient to control active infection) foster the development of myeloid-derived suppressor cells, which inhibit T cells and prevent them from excessive targeting of infected stem cells.
By lowering TNF levels, anti-TNF drugs (like etanercept) support the development of macrophages, DCs and PMNs, thus restoring the functions of T cells (22) and probably allowing a better control of silent infection within stem cells.

important), several mechanisms have emerged to explain the immunosuppressive effects of TNF-alpha, such as the induction of lymphocyte apoptosis, inhibition of TCR signalling and dendritic cell function, or activation of Treg cells (22, 82-83). It should also be recalled that, whereas TNF-RI has only pro-inflammatory effects, the anti-inflammatory action of TNF-RII has been demonstrated in models of arthritic mice transgenic for human TNF (84).
Finally, recent studies concluded that TNF-alpha plays a fundamental role in promoting an immunosuppressive environment just around the target of inflammation (Fig. 1) (22). This could explain why some pathogens like mycoplasma force the infected cells to secrete TNF-alpha (85), as it might favour their persistence due to the locally induced immuno-suppression. Other bacteria like *Salmonella* (86), *Staphylococcus aureus* (87) or *Pseudomonas aeruginosa* (through its flagellin) (88) also recruit immature myeloid cells to benefit from their immunosuppressive properties (86, 88). Similar observations have been made concerning viruses (89). Quite interestingly, in an *in vivo* mouse model of chronic inflammation, the TNF-blocker etanercept enhanced the maturation of immature myeloid cells into dendritic cells and macrophages and restored their immune functions (Fig. 1) (22). In a simian model, adalimumab did not affect levels of simian immunodeficiency virus RNA in peripheral blood or lymph node T cells, while it reduced lymphoid tissue immunopathology and allowed better preservation of $CD4^+$ T cells (90). Thus, anti-TNF agents might sometimes prevent rather than favour the revival of dormant bacteria and viruses and thereby could help to contain some pathogens in their niches (91).

Targeting excessive autoimmune responses and eliminating latent infections from stem cell niches are not mutually exclusive and might rather be synergistic

The possibility that anti-TNF could act as anti-infectious agents in certain environments like the bone marrow should remind us that other drugs given in inflammatory rheumatisms also have anti-infectious properties. Auranofin restricts the viral reservoir of HIV in a monkey AIDS model, inducing containment of the viral load (92). Leflunomide is active against CMV (93) and polyoma BK virus (94). Hydroxychloroquine, besides its previous use to treat malaria, is added to several antibiotics to clear some lasting infections like Whipple's disease (95) or Q fever (96). Sulfasalazine was first used as an antibiotic (97).
Several antibiotics have been tried in RA, including roxithromycin (98) which gave promising results in a recent randomised, double blind study in 100 Turkish RA patients: among those treated with 300 mg roxithromycin for 6 months, an ACR 20 response was achieved in 60% (*vs*. 34%), an ACR 50 response in 38% (*vs*. 12%) and an ACR 70 response in 18% (*vs*. 2%) (p=0.003) (98). However, nearly all previous attempts were negative, while a meta-analysis of similar trials in patients with reactive arthritis concluded that the efficacy of antibiotics was uncertain with no significant effects on joint counts, pain or global scores (99). As already discussed, this nevertheless does not rule out a role of latent bacteria since long term antibiotics tend to enhance the survival of such pathogens (20). Another barrier to curing infection-driven arthritis with antibiotics may be (besides many undesirable effects on microbiota which modulate Treg homeostasis) suboptimal anti-retroviral or anti-bacterial drug concentrations in sanctuary sites like gut-associated lymphoid tissue, lymph nodes and tissue macrophages, as already recognised for the treatment of HIV (100). For all these reasons classical antibiotics are not the solution for dormant bacteria and their use should be discouraged.
Anti-TNF might allow a better control of some dormant bacteria and/or viruses in stem cells, through their enhancement of the maturation of immature myeloid cells around the infected cells (22). The lasting remission of RA or SpA sometimes observed after stopping anti-TNF drugs (101) would corroborate with a sustained effect of these drugs on infected memory or stem cells. The clearance of infectious agents from stem or memory cells could be accelerated by using highly selective methods

like nanodevices specific for dormant infection, combined with new classes of intracellular antibiotics (or anti-viral agents), as already planned for chlamydiae infection (102). The combined use of so-called immunosuppressive therapies and anti-bacterial or anti-viral antibodies has proved be more efficient to clear some pathogens, for example hepatitis B virus (HBV) in HBV-associated polyarteritis nodosa (HBV-PAN), where combining immunosuppression, plasma exchange and an anti-viral drug facilitates sero-conversion and prevents the development of the long term hepatic complications of HBV infection (103).

Further studies on how each bacterium or virus tries to escape the immune response and/or uses TNF to survive in host cells (including stem cells) will certainly be useful, especially as the bacteria and viruses contributing to the pathogenesis of SpA and RA might behave differently from other pathogens. A closer look at the effects of anti-TNF on immunosuppressive myeloid-derived suppressor cells (which also contribute to myelodysplasia) (104), and on chronic latent viral or bacterial carriage by the epiphyseal bone marrow or mesenchymal stem cells of RA and SpA patients, could equally help to unravel the pathogenesis of these disorders and of intermediate disorders like psoriatic rheumatism. A favourable effect of anti-TNF on dermic mesenchymal cells has already been observed in psoriasis, and these cells could also be the first to become involved in the psoriatic process (105). The same might hold true for epiphyseal bone marrow stem cells in psoriatic arthritis, since dysfunction of bone marrow mesenchymal stem cells has been observed in psoriatic patients, with aberrant proliferative activity and an increased apoptosis rate (106).

Conclusion

In most animal models of arthritis, autoimmune processes do not develop under germ free conditions and/or are much worsened when the animals are exposed to pathogens. Although a shift in the microbiota in the gut or lung mucosa and their draining lymph nodes might be sufficient to induce and sustain autoimmunity in SpA and RA, it would still be worthwhile to search for low-grade subclinical infections in stem cells or other memory cells from epiphyseal bone marrow niches, instead of in synovial cells as previously done. Indeed, many viruses and dormant bacteria can use stem cell niches as reservoirs and their sub-clinical transient revival could contribute to autoimmunity in RA and SpA through several mechanisms, including the conversion of resident Tregs to a Th17 phenotype. The improvement in RA after rituximab infusion is consistent with the ability of RTX to clear EBV from the blood and cure atypical EBV infection (71), since the improvement in DAS-28 scores following RTX is significantly higher in patients with a positive baseline PCR for EBV (44). Although mostly considered to be immunosuppressive drugs enhancing the risk of systemic infection, anti-TNF could also prevent the revival of some dormant bacteria or viruses within stem cell niches. Thus, in an *in vivo* mouse model of chronic inflammation, the TNF-blocker etanercept stimulated the maturation of myeloid-derived suppressor cells from stem cell niches into dendritic cells and macrophages and restored their immune functions (22). Therefore, targeting excessive autoimmune responses and eliminating latent infections from stem cell niches are not mutually exclusive goals, and could in fact be highly synergistic.

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