Advances in understanding the pathophysiology of spondyloarthritis

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Abstract (150 words – non structured)

Progressive understanding of the underlying pathophysiology of axial spondyloarthritis has successfully translated into innovative therapeutic strategies and successful management of patients in the clinic. This review summarizes the key roles of pro-inflammatory cytokines tumor necrosis factor and interleukin-17 in the onset and progression of disease and how these cytokines are instrumental in shaping the concept that enthesitis is a key feature of axial spondyloarthritis. Advances in immunological technologies have lead to the important insight that different cell populations, part of both the innate and adaptive immune system, play a key role in axial spondyloarthritis. Besides inflammation, structural damage to the axial skeleton, in particular progressive ankylosis of the sacroiliac joints and the spine, is key to the outcome of patients. Novel data integrate the role of pro-inflammatory cytokines and enthesitis in this context.

Keywords: axial spondyloarthritis, spondyloarthritis, ankylosing spondylitis, bone, cartilage

Spondyloarthritis refers to a disease concept that comprises different diagnostic entities [1, 2]. Currently, predominant axial disease is clinically distinguished from predominant peripheral skeletal disease [3, 4], a paradigm supported by the differential efficacy of some drugs on the presenting symptoms of the disease complex [1, 5, 6]. Within the axial disease group both ankylosing spondylitis and non-radiographic axial spondyloarthritis are identified and distinguished by the presence or absence of radiographic lesions, in particular progressive ankylosis of the sacroiliac joints and the spine [1]. The pathophysiology of spondyloarthritis remains a complex puzzle of which the clinical and research community currently knows many pieces and that are slowly but steadily being brought together. Over the last years, insights into the different mechanism of disease have transformed clinical concepts of the disease, have led to the identification of different therapeutic targets and contributed to the development of specific and often highly successful strategies. Therefore, the outlook of patients suffering from spondyloarthritis has dramatically changed [1, 6].

Effectively, the daunting image of young patients rapidly evolving from the first signs of inflammatory back pain towards a disabling ankylosis of the spine is gradually replaced by a much more optimistic view on disease control and prevention of loss of function and structural damage. This conceptual progress is largely based on the integration of basis, translational and clinical scientific knowledge and likely shows the road forward towards even better management of the disease and outlook for the patients.

In this narrative review, evolving insights into the pathophysiology of mostly axial spondyloarthritis are discussed and put into a broader clinical perspective. Indeed, progress in the management of spondyloarthritis should be further based on such an integration of knowledge, to the benefit of the patients.

A – From symptoms to mechanism of disease

Our understanding of spondyloarthritis has come a long way from describing the cardinal symptoms of joint inflammation, warmth, swelling, pain, redness and loss of function, towards increasing insights into mechanisms of disease at the tissue, cell and molecular level **(Figure 1)**. The translation of symptoms into mechanisms of disease has paved the way

towards the introduction of new therapies. Inflammation, in particular, in spondyloarthritis is increasingly well understood with the identification of key cytokines and immune cell populations that are involved in the disease process. The best examples are obviously the key role of cytokines tumor necrosis factor (TNF) and interleukin-17 (IL17). Antibodies or soluble receptors directed against these cytokines now feature prominently as highly effective therapeutic strategies for patients with either axial or peripheral spondyloarthritis [1, 6].

Similarly, insights into the mechanisms responsible for joint destruction have grown at a strong pace. This foremost includes the identification of the osteoclasts as the principal bone destructive cell and the molecular elucidation of its differentiation from monocytic precursors and progressive maturation towards a multinuclear giant cell [7]. Again, the identification of the RANK/RANKL/OPG system as key intercellular signaling molecules in this process, has permitted the development of potent drugs such as antibodies directed against RANKL that are highly effective in reducing systemic bone loss [8]. In addition, the identification of cartilage tissue destructive enzymes such as matrix metalloproteinases and ADAMTS enzymes [9] may open up opportunities for therapeutic intervention, although initial attempts were marred by toxicity issues [10].

Progressive ankylosis of the sacroiliac joint is a cardinal feature of disease in many patients with spondyloarthritis. In contrast to the processes mentioned above, inflammation and tissue destruction, knowledge of the molecular and cellular mechanisms of new tissue formation in a disease context remains limited. Growth factor cascades such as bone morphogenetic proteins and Wnts have been associated with the process of new bone formation [11-13] and the relationship between inflammation and new bone formation has been heavily debated [14-17]. Nevertheless, there is currently no unifying view on how to specifically address this important and clinically relevant issue by a therapeutic strategy.

A – integration of knowledge is key towards better understanding of pathophysiology

Important insights into a disease like spondyloarthritis are rarely based on a single piece of evidence. Rather, data from different fields are coming together and complement each

other in such a process **(Figure 2)**. The rapid evolution of genetics research since the introduction of genome wide association studies and the use of next-generation sequencing approaches has strongly contributed to the better understanding of disease [18-20]. The integration of multiple susceptibility genes into a network concept or the specific identification of a potential therapeutic target has often prompted the initiation of further studies to identify precise roles and mechanisms of disease. In such a setting mouse and rat models have been particularly important and complement translational studies using human serum samples or tissue biopsies. Finally, the best evidence for a mechanism to be important in a disease such as spondyloarthritis are the data coming out of randomized clinical trials demonstrating the efficacy of a given therapeutic strategy.

In patients with axial spondyloarthritis such clinical trials and the subsequent clinical experience after introduction of specific drugs into the market, have demonstrated that anti-TNF and anti-IL17 are highly effective in treating signs and symptoms of disease [1, 6]. The efficacy of anti-TNF and anti-IL17 has also been directly or indirectly demonstrated for patients with peripheral spondyloarthritis [21, 22]. Interestingly, anti-p40, a peptide chain shared by IL12 and IL23 [23], as well as anti-IL23 [24] have been shown to be effective in patients with psoriatic arthritis, a common chronic joint disorder that is usually positioned within the spondyloarthritis concept. However, specific targeting of IL-23 in a randomized controlled trial did not appear to be effective for axial disease [25]. In addition anti-TNF, anti-IL17, anti-p40 and anti-IL23 are effective in treating the skin disease psoriasis [26] and anti-TNF as well as anti-p40 are effective in the management of inflammatory bowel disease [27], two comorbidities as well as individual diseases closely related to and aligned with the spondyloarthritis concept.

A – A tale of cytokines: TNF and IL17

Preliminary evidence that TNF may play a role in spondyloarthritis was based on the analysis of tissue biopsies obtained from the sacroiliac joints of patients with ankylosing spondylitis [28] and some observations that serum levels of TNF may be increased in this patient group [29]. Moreover, the observations that signs of arthritis and spondylitis were improving in patients with inflammatory bowel disease and associated spondyloarthritis [30] provided

additional evidence to launch specific clinical trials for patients with ankylosing spondylitis [31, 32]. Since then, anti-TNF has become the reference biological treatment strategy in this population. Further evidence corroborating the essential role of TNF in this disease, was found in the TNFdARE mouse model [33, 34]. In these transgenic mice, the AU-rich element (ARE) within the TNF gene is deleted. This ARE element plays an important role in TNF biology as it renders the message RNA for this cytokine unstable. As a pro-inflammatory cytokine with key roles in the defense against infections, TNF can be rapidly upregulated and expressed in high amounts. However, the presence of the cytokine in the inflammatory reaction may have additional damaging effects on the own tissues and boost an inflammatory reaction that is so strong that it becomes damaging rather than defensive. Therefore, the ARE element serves as a regulatory mechanism that limits the lifetime of the TNF mRNA thus limiting its effects [35]. In the absence of this element, the mRNA is stabilized and this results in a functional overexpression of the gene in those sites where the cytokine is endogenously upregulated. In the mouse, this unique approach towards functional overexpression results in arthritis, enthesitis, sacroiliitis and inflammatory bowel disease, all features associated with human spondyloarthritis [33, 34].

The IL17 family, comprising IL17A to IL17F, is a group of structurally related cytokines that has only recently been identified [36]. The cytokines define a novel subset of T helper (Th) cells, the key T cell population that is essential in the cellular and humoral adaptive immune response. The Th17 population is particularly important in the defense against fungi. It complements the two other key Th axes [37]: Th1 cytokines including interferons and TNF, important in the defense against intracellular pathogens and the Th2 cytokines including IL4 and IL5 and key players in the defense against extracellular parasites. The differentiation of these respective T cell populations is directed by specific cytokine programs associated with antigen-presenting cells: IL12 for the Th1 cells, IL4 for the Th2 cells and IL23 for the Th17 cells [37].

The attractiveness of the T helper cell paradigm and the relatively simple access to human T cell populations that can be isolated from a simple blood sample, may easily hide the more complex role and the multiple sources of IL17 as a key inflammatory cytokine **(Figure 3)** [38, 39]. Effectively, in addition to the master regulators of the adaptive immune responses

including both CD4 helper and CD8+ cytotoxic cells, a number of cells mostly belonging to the innate immune system, can produce IL17 [38, 40, 41]. These include neutrophils, mast cells, macrophages, gamma-delta T cells, innate lymphoid cells type III, Natural Killer (NK) and NK T cells [36, 38-41]. Many of these cell populations belong to the so-called tissue resident immune cells that may not circulate in the body but rather orchestrate inflammatory reactions within the tissues that are involved in spondyloarthritis such as the enthesis and the synovium. Effectively, neturophils and myeloid precursor cells have been demonstrated to produce IL17 in both the HLA-B27 transgenic rat model of spondyloarthritis [39] as well as in the affected facet joints of patients with axial spondyloarthritis [42].

A cell type of particular interest are the mucosal-associated invariant T (MAIT) cells, a cell population that can be positioned at the intersection of innate and adaptive immunity and that can produce IL17A as well as TNF in a T-cell receptor dependent or independent way [43]. Gracey *et al* recently reported on MAIT cells and their functional phenotype in patients with axial spondyloarthritis, in particular ankylosing spondylitis [44]. They suggest that a relative abundance of IL-17-producing MAIT cells is present in AS in the circulation as well as in the joints, assessed by synovial fluid analysis in comparison to numbers in healthy donors and in patients with rheumatoid arthritis. The small but disease-associated IL17 positive population in ankylosing spondylitis patients is further complemented by a larger proportion of TNF and IFN producing MAIT cells [44], thus associating the MAIT population with the key cytokines linked to the disease. Further research will likely focus on the migration of such cells from the gut towards the affected joints and on the key question whether these cells acquire their specific phenotype in the disease affected tissues [44].

Downstream effects of IL17 may include a large group of target cells that upon IL17 stimulation further contribute to inflammatory and tissue remodeling reactions **(Figure 3)** [36]. These cells include macrophages, neutrophils, keratinocytes, endothelial cells, fibroblasts, chondrocytes, osteoblasts and osteoclasts. IL17 stimulation of macrophages and neutrophils may trigger the further production of other pro-inflammatory cytokines including IL1, IL6, IL8 and TNF [36, 39]. Keratinocytes may also produce such cytokines as well as chemokines that further boost the attraction of other inflammatory cells into the

skin in a positive feedback loop that is typical for psoriasis, the skin disease that is clinically and genetically linked with spondyloarthritis [26, 38].

TNF can be targeted today by a number of antibodies (infliximab, adalimumab, golimumab), modified antibodies (certolizumab pegol) and a soluble receptor (etanercept). Over 15 years of clinical experience beyond the initial clinical trials has firmly established anti-TNF therapies as a cornerstone of management of disease for many patients with moderate to severe spondyloarthritis [45]. Similarly, antibodies against IL17A have found their way to the clinic in the management of spondyloarthritis or psoriatic arthritis (secukinumab and ixekizumab). More options and alternatives may be on the horizon. Indeed, the IL17 family does not only include IL17A (composed of two IL17A chains), but also IL17F (2 IL17F chains) and a dimeric IL17AF form (one IL17A and one IL17F chain) [36]. In addition to anti-IL17A blocking, the effects of combined targeting of IL17A and F are currently under investigation in clinical trials [46]. Other options may include blocking of the IL17 receptor, but this strategy has been associated with potentially severe adverse events including suicide although no causal or consistent relation could be defined [47]. Interestingly, also dual TNF and IL17 inhibitors are under clinical development [48].

In addition, the list of cytokines being targeted for axial spondyloarthritis, may still expand. A recent study by the group of Paul Bowness, Oxford, UK demonstrated a large number of GM-CSF positive and GM-CSF/IL17 double positive lymphocytes in spondyloarthritis patients [49]. Interestingly the production of GM-CSF appeared to be dependent on G-coupled protein receptor 65 (GPR65), a proton-sensing receptor associated with spondyloarthritis in genome-wide association studies [50].

A – the anatomic basis of disease: the "enthesitis"-concept revisited

The successful targeting of key cytokines cannot explain the specific development of inflammation at given sites in spondyloarthritis. Indeed inflammation occurring at the sacroiliac joints and spine, and eventually some peripheral joints should be further investigated to gain in depth understanding of the disease processes. Recent advances

provide further support that the key to this issue may be found in the concept that enthesitis is a defining mechanism of disease in spondyloarthritis [51-54].

Based on clinical, pathological and radiological observations, Ball historically proposed the enthesis as a unifying factor in axial spondyloarthritis [51]. The enthesis refers to the specific anatomical zone where tendon and ligament fibers insert into the underlying bone. It forms a multilayered structure that conveys the tissue its strong mechanical strength. Tendon and ligament fibers move through a zone of non-calficied fibrocartilage, then through calcified fibrocartilage and subsequently into the underlying bone [53]. The cartilage bone interface is irregular rather than linear thereby increase the contact surface. In the context of spondyloarthritis, enthesitis can be a presenting symptom, e.g. at the insertion of the Achilles tendon or the *fascia plantaris*, but also a disease mechanism that subsequently evolves into arthritis, enthesitis and eventually osteitis [53, 55].

The original observations by Ball and other pioneers in the field were further corroborated decades later by the work of Dennis McGonagle at Leeds University, UK and the late Michael Benjamin, University of Wales, UK. By combining imaging and pathology studies they demonstrate how enthesitis is a unifying disease mechanism that defines spondyloarthritis and that help distinguish the disorder from other chronic inflammatory joint disease such as rheumatoid arthritis [52, 53]. Careful analysis of the microanatomy of the enthesis also contributed to the definition of the synovio-entheseal complex [53]. The close proximity and direct connection between the connective tissue of enthesis and bone on one hand and the loose connective tissue of synovium and bone marrow, lead to the hypothesis that chemotactic signals out of the enthesis would lead to the accumulation of inflammatory cells in these adjacent tissue that have a strong propensity for inflammatory cell infiltration and accrual.

The initial concept within this paradigm suggested that the enthesis itself would not be an immune-priviledged site and that cells were unlikely to infiltrate the connective tissues of this fiber- and extracellular matrix-rich attachment zone. However, an intriguing study from 2013 fundamentally challenged this concept. Sherlock et al discovered, within the mouse enthesis, a small population of IL23 receptor, CD3 positive T cells [56]. Remarkably these T

cells are negative for conventional T cells markers CD4 and CD8 but are positive for transcription factor ror-gamma-t, essential in the differentiation of Th17 cells. Effectively, systemic overexpression of IL23 activates these entheseal T cells and leads to increased IL17 production, a feature associated with the development of arthritis, enthesitis and new bone formation in affected joints [56, 57]. Data from this study were more recently confirmed by independent investigators and the T cell population further characterized as gamma-delta T cells, most likely originating in the thymus [57]. Obviously access to human tissue samples of the enthesis is a big challenge, but an interesting study from the group of Dennis McGonagle provided solid evidence that a similar cell population can be found within the human enthesis [58]. The identified IL23-receptor positive cells were not demonstrated to be T cells but rather type III innate lymphoid cells, again positive for the IL23 receptor and able to produce IL17 [58].

The identification of entheseal cells responsive to IL23 and producing IL17 gave rise to a new paradigm in which entheseal immune cell populations are key hubs for disease development [59, 60]. Nevertheless, the factors that trigger the response of these cells in humans remain elusive. The enthesis is not a barrier tissue with the outside world, unlike the skin and the intestine, so the role of T cells in the enthesis in host defense remains ill-defined. Interleukin-23 production could be linked to HLA-B27, the main genetic risk factor for axial spondyloarthritis [20]. This specific HLA antigen has been linked with misfolding and an activation of the unfolded protein response which can lead to IL23 production, or by interactions of HLA-B27 with killer immunoglobulin receptors (KIR) on immune cells, again potentially leading to IL23 production [61]. IL23 could also reach the entheseal immune cells from distant sites of inflammation. The number of SpA patients with subclinical gut inflammation as well as active inflammatory bowel disease remains debated but this could provide an indirect trigger for the entheseal cells [62-64]. The same principle can be applied to psoriasis. However, in skin-specific IL17 transgenic mice no arthritis was demonstrated despite clear systemic effects of high IL17 levels in the skin on bone loss of bone density [54].

IL23 could also be produced locally as part of the tissue's response towards biomechanically induced microdamage [33, 54]. Obviously the transition tissues of the enthesis organ are

exposed to biomechanical stress, and this may link damage with local IL23 production. A role for entheseal T cells or ILCs in the tissue repair response would also provide an explanation for the presence of these cells in the enthesis. This concept fits with the increased attention towards tissue resident immune populations with important roles in the maintenance of tissue integrity and would identify the IL23R positive cells in the enthesis as sentinel cells [54, 60]. The suggested downstream events include increased secretion of IL17 and TNF, although all cellular sources in these processes have likely not yet been defined. The existence of positive feedback loops involving these cytokines and their source cells is put forward to understand the amplification of the inflammatory reaction and the progressive development of chronic and sustained inflammation.

Data from different rodent models support the concept of enthesitis described above. Enthesitis has effectively been demonstrated to be the primary disease manifestation in the TNFdARE mice that closely mimics the patterns of disease that can be seen in patients with spondyloarthritis [33, 34]. Of note, in the sustained presence of high levels of TNF, signs and symptoms caused by inflammation may mimic aspect of spondyloarthritis, yet no signs of new bone formation that could eventually lead to ankylosis are recognized [33]. However, enthesitis can also be a dominant feature in mouse models that are TNF-independent such as the myeloid specific A20 knockout mice [65]. A20 is an intracellular inhibitor of NFkB activation, which is a key driver of acute and chronic inflammation. Both anti-IL17 and anti-TNF are effective in preventing disease in HLA-B27 transgenic rats, in a preventive as well as a therapeutic setting [66, 67]. However, targeting IL-23 does not appear to be effective once disease has been established [68].

The spontaneously occurring arthritis in aging male DBA/1 mice is mostly characterized by new bone formation leading to ankylosis but also by transient acute inflammation surrounding the enthesis [69]. The model develops upon grouped caging of aged male DBA/1 mice. In this model, treatment with etanercept failed to reduce the severity of the clinical signs of disease as well as the new bone formation process leading to ankylosis that characterizes the affected joints [70]. In contrast, anti-IL17 strategies were shown to be effective in reducing clinical signs of disease as well as the new bone formation process [71]. These data do not allow to conclude that TNF and IL17 inhibition would have distinct

outcomes in human spondyloarthritis patients but rather that mouse models of disease can be either IL17 or TNF dependent.

A - structural damage in spondyloarthritis

The paradigmatic image of structural damage to the skeleton in patients with spondyloarthritis is that of the progressive spinal ankylosis leading towards loss of mobility in the spine and a fixed posture. The molecular and cellular mechanisms underlying these sometimes dramatic processes remain largely unknown with limited information available from patient materials and with the available animal models limited in their translational value due to the quadrupedal gait of the rodents compared to the bipedal gait of man [14]. Progressive ankylosis, even when spectacular is not the unique feature of structural damage in patients with spondyloarthritis. Bone erosive disease is relatively rare with the exception of erosive changes in the sacroiliac joints and in peripheral joints of patients with psoriatic arthritis, but systemic bone loss leading to decreased bone quality is very common and may lead towards osteoporotic fractures [72].

Pathology studies in mouse models and to a lesser extent in human tissue samples suggest that syndesmophyte and osteophyte formation in disease is largely following the endochondral bone formation process [54]. In this sequence of events, progenitor cells from the periosteum or synovium first proliferate, condensate and then undergo chondrogenic differentiation building up a cartilage template that is then subsequently invaded by bone and osteoprogenitor cells [73]. In the final steps the cartilage template is replaced by bone. Mouse models indicate that the molecular signaling pathways underlying these processes are similar to those that play the key roles during skeletal development and growth. These pathways include bone morphogenetic proteins (BMPs) [11], Wnt signaling [12] and Hedgehog signaling [74]. Effectively, modulation of such pathways in mouse models of joint ankylosis can reduce or prevent the pathological process.

However, the impact of the inflammatory cytokines that are key to the development of inflammation in spondyloarthritis is less clear. Different in vitro and ex vivo setups have lead to inconsistent results [13, 14]. In general, both TNF and IL17 appear to negatively affect the

bone differentiation process, thus not explaining directly the link between inflammation and new bone formation that is characteristic for spondyloarthritis. In contrast, both TNF and IL17 are well known to stimulate osteoclast driven bone loss by stimulating the differentiation and maturation of osteoclasts. Taking into account the slow effects of anti-cytokine strategies in patients with spondyloarthritis, the inflammation-associated bone loss has been proposed as a driver of the pathological bone formation process [75]. In vertebral bodies or sacroiliac joints, osteitis will lead to net bone loss and this has an impact on the mechanical stability of the skeletal element. In the continued presence of inflammation, the normal bone remodeling cycle cannot compensate for this bone loss as inflammation acts as a negative regulator of osteogenic differentiation and activity of the cells. Yet, the syndesmophyte formation provides an alternative strategy and location for a stabilizing effort, similar to what can be seen in fracture repair or in osteoarthritis where changes in the biomechanical stability of the contact surfaces also triggers a new bone formation process. This hypothesis emphasizes that the skeleton seeks biomechanical stability can thus be applied to different diseases and situations with the notable exception of rheumatoid arthritis in which little or no joint remodeling and repair is seen, even with sustained control of inflammation [75]. The direct stimulatory effects of auto-antibodies that are highly prevalent in rheumatoid artritis (anti-citrullinated protein antibodies) may explain this difference [76, 77].

Nevertheless, the biomechanical stability concept provides a good explanation why it takes sustained control of inflammation to prevent structural disease progression [78-80] and also theoretically explains that existing structural damage is a risk factor for further progression as an ankylosed segment will affect the stability and biomechanical stress of other segments positioned above or beneath within the spine.

A – Conclusion

Current treatment paradigms are increasingly supported by detailed insight into the immunopathology of axial spondyloarthritis. Better understanding of the involved cell populations and regulatory mechanisms may provide an inroad towards more personalized medicine approaches for this disease and towards better fine-tuning of new drugs. In

addition, insights into the disease localization and the structural consequences of disease aids daily management of the patients and the design of novel clinical trials.

A – Acknowledgements – conflicts of interest

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A - Practice points

- the use of anti-TNF and anti-IL17 strategies in the management of patients with axial spondyloarthritis is backed up by solid biological data.
- sustained suppression of inflammation in patients with axial spondyloarthritis appears to limit structural disease progression, thus resulting in full disease modification.
- Enthesitis is not only a clinical sign of disease in patients with spondyloarthritis but also provides the biological basis for a concept of the disease pathogenesis.
- Systemic bone loss, predisposing to fractures, should be taken into account in the clinical management of patients with axial spondyloarthritis.

A - Research agenda

- Further identification of tissue resident immune cells and their eventual migration between tissues may allow to specifically target "pathogenic" cells in patients with axial spondyloarthritis.
- The role of IL23 as upstream driver of IL17 production is far from understood, in particular in axial disease as anti-IL23 strategies do not appear to be successful for the treatment of these spondyloarthritis patients.
- Sustained efforts towards collection of translationally relevant tissues such as the enthesis and the synovium provide extremely valuable resources for further research.

- Integration of genetics, translational studies and novel types of clinical trials should pave the road towards better personalized medicine in the management of patients with axial spondyloarthritis.

A – Figure legends

Figure 1: The signs and symptoms of arthritis are caused by distinct processes in the joint. Synovitis with extensive inflammation is characteristic. Formation of pannus tissue and activation of osteoclasts contributes to joint destruction. Tissue remodeling is characterized by new cartilage and bone formation eventually leading to ankylosis. The images presented were obtained from mice with methylated bovine serum albumin-induced arthritis (inflammation and destruction) and from mice with spontaneous ankylosing enthesitis (remodeling). (reproduced from [81]).

Figure 2: Insights into the pathophysiology of axial spondyloarthritis are based on the integration of different datasets (images used from Servier Medical Art licensed under a Creative Commons Attribution 3.0 Unported License).

Figure 3: IL17 can be produced by different immune cell populations and has many different cell types as potential targets.

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