Pathophysiology of axial spondyloarthritis: Consensus and controversies

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Received: 20 December 2017 | Accepted: 14 February 2018

DOI: 10.1111/eci.12913

REVIEW

WILEY

Pathophysiology of axial spondyloarthritis: Consensus and controversies

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Abstract

Background: Axial spondyloarthritis (axSpA) is a common inflammatory arthritis of the sacroiliac joints and the spine. The best-known and most studied form of axSpA is ankylosing spondylitis.

Design: In this review, we provide a brief overview of the pathophysiology of axSpA. In addition, we performed a quantitative text analysis of reviews on the pathogenesis of axSpA published in the last 10 years to establish the current consensus in various fields of research into the pathogenesis of axSpA.

Results: There appears to be broad consensus on genetic risk factors and the involvement of the immune system in the initiation phase of the disease although little consensus was found on which specific immune cells drive disease. Moreover, despite relatively little data available, alterations in the microbiome are commonly thought to be involved in disease. Abnormal bone formation is the most prominent pathogenic factor thought to be involved in disease progression.

Conclusion: So, although the pathophysiology of axSpA remains incompletely understood, the progress in recent years in several fields of research in axSpA including genetics, diagnosis, imaging and therapeutics, hold great promise for the future.

KEYWORDS
axial spondyloarthritis, early disease, pathogenesis

1 | INTRODUCTION

Axial spondyloarthritis (axSpA) is an inflammatory arthritis of the sacroiliac (SI) joints and the spine. The best-known and most studied form of axSpA is ankylosing spondylitis (AS), also called radiographic axSpA, which is characterized by sacroiliitis on radiographs according to the modified New York criteria. The other form of axSpA, nonradiographic axSpA, is characterized by the absence of radiographic sacroiliitis but inflammation on MRI of the SI joints is frequently visible.[1]

AxSpA is a multigenetic disease characterized by back pain and in a substantial number of patients, excess bone formation.[2] Arthritis and enthesitis are the most common peripheral manifestations, which can occur at any time in the course of the disease. Arthritis typically affects the large joints in the lower limbs. Inflammation at the insertion of tendons, ligaments or capsule into bone is called enthesitis. It has been hypothesized that inflammation in axSpA starts here.[3] A less common manifestation is dactylitis, which is a swelling of a finger or toe into a sausage shape due to tendovaginitis. Common extra-articular manifestations are acute anterior uveitis, inflammatory bowel disease and psoriasis (Figure 1).

A recent systematic literature review reported a prevalence of AS of 0.24% in Europe and 0.17% in Asia with an estimated number of patients of 1.3-1.6 million in Europe and 4.6-5.0 million in Asia. Estimated prevalence rates of AS are 0.32% in North America, 0.10% in Latin America and 0.07% in Africa.[4]

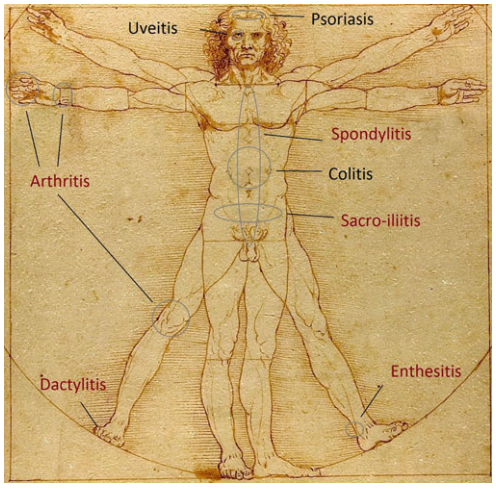

FIGURE 1 Multiorgan involvement in spondyloarthritis shown on Leonardo da Vinci's *L'Uomo Vitruviano*

In the last 10 years, significant progress has been made in dissecting the genetic background of the disease.[5] Also, the potential role of microbial triggers and the molecular pathways involved in excess bone formation are areas of active research. Furthermore, progress has been made in identifying nonradiographic axSpA. The 2009 ASAS axSpA classification criteria[6] were the first to give the same weight to sacroiliitis on MRI as to sacroiliitis on radiographs, and this classification set has been used to perform clinical trials in nonradiographic axSpA.

In this review, we provide a general overview of the pathophysiology of axSpA. In addition, we performed a quantitative text analysis of reviews on the pathogenesis of axSpA published in the last 10 years to establish the current consensus in various fields of research into the pathogenesis of axSpA.

2 | LITERATURE SEARCH AND ANALYSIS

The literature search strategy focused on reviews of pathogenesis of axSpA published in the last 10 years. For the 2 main topics: axial spondyloarthritis and pathogenesis, a large number of relevant keyword variations were used, both in the controlled vocabularies of the various databases as well as free text word variations. Results were limited to review articles written in the English language and published from the year 2006 onwards. For the complete search strategies, see Data S1.

Two reviewers (AdK and FvG) individually screened article titles and abstracts. An article was included if it was a review regarding the pathogenesis of axSpA. In cases of disagreement between reviewers, consensus was sought through discussion.

Full article texts including title page and abstract were reviewed by 1 reviewer (AdK) for statements mentioning a pathogenic factor or mechanism. Relevant statements were assigned a keyword, preferably a single noun, and a statement on disease phase (initiation, progression, not specified) as described by the author. For example: "IL-23 acts on double-negative enthesis-resident T cells which initiates enthesitis." In this example, the keyword would be "IL-23" and the disease phase "initiation." Choice of keywords was free and could be altered at any point during the text review process. The probable causality according to the original author (likely, possible, unlikely and uncertain) was also recorded but statements other than "likely" and "possible" were rare (data not shown). Next, each article was assigned to an individual author based on the first or last author of the article. Subsequently, to compensate for 1 author publishing multiple reviews, the number of times a pathogenic factor or mechanism with the same keyword was used by the author was reduced to 1, that is if an author published 4 articles on the role of ERAP1, the keyword "ERAP1" was counted once for that author instead of 4 times. For each keyword, the number of times different authors proposed it as a pathogenic factor in axSpA in recent literature was counted. Disease phase was assigned to each keyword based on the majority of authors (in case of a tie the "not specified" phrase was used).

Four hundred and eighty unique articles were identified. Based on the titles and abstracts (n = 101), and consensus through discussion in cases of disagreement (n = 13), 114 articles were included. Full text was available for 98 of these 114 articles in the Leiden University Medical Center. Based on the full text, an additional 5 articles were excluded from the analysis because they were either not about axSpA (n = 2), a meta-analysis (n = 1), a comment on an article (n = 1) or because they only presented genetic association data without a hypothesis about the possible role of the described factor in the pathogenesis of axSpA (n = 1). In the 93 selected review articles, 70 keywords were identified. Thirty-eight were used by 1 author and 32 were used by more than 1 author (Table 1).

3 | GENETICS

AxSpA rarely starts after the age of 45 years and is highly heritable. A study from Iceland showed a significantly increased risk for relatives of the patients with AS to develop AS with a relative risk for first-, second- and third-degree relatives of 75.5, 20.2 and 3.5, respectively.[7] One study calculated that based on published data the risk of disease in family members of axSpA patients is 63% in monozygotic twins, 8% in first-degree relatives, 1% in second-degree relatives and 0.7% in third-degree relatives[8]).

TABLE 1 Keywords extracted from review articles on the pathogenesis of axial spondyloarthritis published in the last 10 y with each keyword counted once per author

Keyword	Count	Rank	Disease phase[a]
HLA-B27	29	1	Initiation
ERAP1	17	2	Not specified
Bone/syndesmophyte formation	14	3	Progression
Microbiome	11	4	Not specified
IL-23/IL-23 gene	8	5	Not specified
TNF-alpha	8	6	Not specified
Genetic risk (unspecified)	7	7	Initiation
Gut inflammation	7	7	Initiation
Enthesitis	6	9	Initiation
T cells	6	9	Not specified
IL-17	5	11	Not specified
B cells	4	12	Not specified
Gut and joint inflammation	4	12	Initiation
HLA-B27 and ERAP1 interaction	4	12	Initiation
IL-1	4	12	Initiation
Mechanical stress	4	12	Not specified
Environmental risk (unspecified)	3	17	Initiation
HLA-B27 and microbiome	3	17	Initiation
Macrophages	3	17	Not specified
PTGER4 gene	3	17	Not specified
Th17 cells	3	17	Not specified
Bone homoeostasis alterations	2	22	Progression
CD8+ T cells	2	22	Initiation
DKK1 signalling	2	22	Progression
HLA-B60	2	22	Initiation
IFN-gamma	2	22	Not specified
IL-23+ Th17-cells	2	22	Not specified
IL-6	2	22	Not specified
NK cells	2	22	Not specified
RUNX3 gene	2	22	Initiation
TLR signalling	2	22	Not specified
Wnt signalling	2	22	Progression

HLA-B27, human leucocyte antigen B27; HLA-B60, human leucocyte antigen B60; ERAP1, endoplasmic reticulum aminopeptidase 1; PTGER4, prostaglandin E receptor 4; RUNX3, runt-related transcription factor 3; IL-1/6/17/23, interleukin-1/6/17/23; IFN-gamma, interferon gamma; TNF-alpha, tumour necrosis factor alpha; NK cell, natural killer cell; DKK1, dickkopf 1; TLR, toll-like receptor.

Keywords that were only used once: "Ankylosis," "ANTXR2,""Autoinflammatory," "Bacteria," "BMP," "CARD15," "CARD9," "Chlamydia," "CYP2D6," "EDIL3," "ERAP2," "Gender," "Gut defences," "HLA-B27 and IL-23/IL-17," "HLA-B27 and inflammation," "HLA-B27 and Th17 cells," "IL-17 IL-23 IL-22 and Th17 cells," "IL-23R," "Immune cells," "Immune system," "Innate immunity," "Joint inflammation," "KIR," "Klebsiella genus," "MICA," "MicroRNA," "MMP," "Myofibroblasts," "PTPN22 and CTLA4," "Smoking," "Stem cells," "Stress," "TIM-3 gene," "TNF-blocker," "TNFRII," "Treg cells," "Type17 cells," "UPR and IFN."

[a]According to the majority of authors.

The most likely mode of inheritance is polygenic with multiplicative interaction among loci.[8] By far, the most important genetic risk factor is human leucocyte antigen (HLA)-B27 and prevalence of HLA-B27 generally mirrors the prevalence of axSpA in a population.[9,10] As HLA-B27 is present in about 70-90% of patients with AS in most ethnic groups, compared, for example 6% of the general population in the United States, it is widely assumed to play a

major role in the pathogenesis of AS (Table 1). The association of HLA-B27 and disease also extends to other forms of spondyloarthritis (SpA), though to a lesser degree. In recent years, extensive progress has been made identifying susceptibility alleles in the disease, with over 100 established loci identified, contributing roughly 10% of the heritability of the disease, over and above the major effect of HLA-B27, which determines approximately 20% of the genetic risk. Indeed, apart from HLA-B27 other genetic risk factors (ERAP1, genetic variation in IL-23, PTGER4, HLA-60 and RUNX3) have been proposed to directly play a role in initiation of disease by several experts (Table 1).

4 | HLA-B27

Several theories have been put forward explaining the role of HLA-B27 in pathogenesis of axSpA. The 3 most prominent theories are the "arthritogenic peptide hypothesis," "the heavy chain homodimer hypothesis" and the "HLA-B27 misfolding hypothesis." These not mutually exclusive hypotheses are illustrated in Figure 2. The first is based on the natural immunological function of HLA-B27 of presenting antigenic peptides to cytotoxic T cells. The arthritogenic peptide hypothesis postulates that there are certain microbial peptides that are very similar to self-peptides that may be presented by HLA-B27. Due to molecular mimicry, reactivity of CD8+ T lymphocytes against HLA-B27-peptide complexes would then lead to autoreactivity and subsequently, to autoimmune disease including arthritis and spondylitis. Although the peptide binding motif of HLA-B27 has been extensively studied, no arthritogenic peptides have been discovered yet. Moreover, in the HLA-B27 transgenic rat model of SpA, disease may develop in the absence of any functional CD8+ T cells making it unlikely classic T cell recognition of HLA-B27 is of primary importance in this animal model.[11]

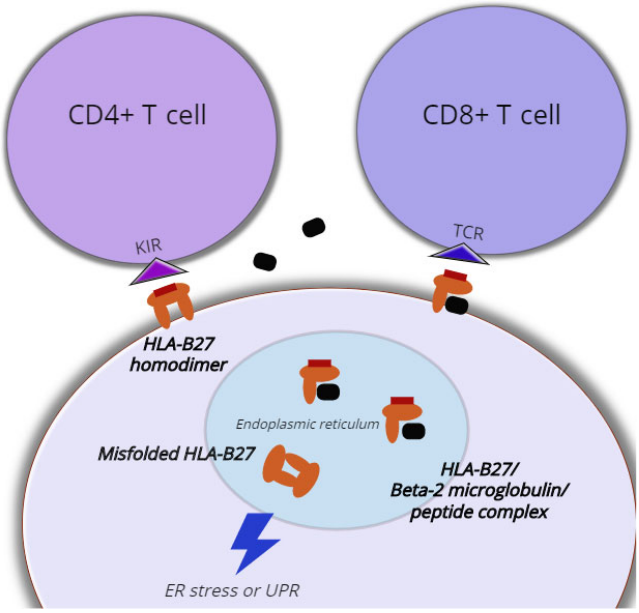

FIGURE 2 Overview of hypotheses explaining role of HLA-B27 in axial spondyloarthritis. A, Arthritogenic peptide hypothesis: Pathogen- or self- derived peptides bound to conventional HLA-B27/beta-2 microglobulin complexes are recognized by autoreactive CD8+ T cells through the T-cell receptor (TCR). B, Cell surface HLA- B27 free heavy chain homodimer expression hypothesis: HLA-B27 free heavy chains including dysfunctional HLA-B27 homodimers are expressed at the cell surface and activate cells bearing killer immunoglobulin-like receptors (KIR) and/or leucocyte immunoglobulin-like receptors such as CD4+ cells or NK cells. C, Misfolded HLA-B27 hypothesis: Misfolding of HLA-B27 within the endoplasmic reticulum (ER) causes an unfolded protein response (UPR) or other form of cellular stress, or autophagy, which has downstream effects on cellular function (eg, excessive IL-23 release)

A second model explaining the association of HLA-B27 with axSpA is based on the observation that HLA-B27 heavy chains can form homodimers without beta-2-microglobulin. It has been shown that these HLA-B27 homodimers can bind leucocyte receptors independent of the sequence of bound peptide.[12] Moreover, peptide-linked HLA-B27 homodimer complexes have been shown to enhance survival, proliferation of KIR3DL2(+) CD4 T cells and increase IL-17 production by these cells ex vivo.[13] IL-17-producing CD4(+) T cells have been reported to constitute a substantial percentage of CD4+ T cells in patients with long-standing disease but have been difficult to detect in recent onset axSpA.[14]

Thirdly, the misfolding hypothesis states that HLA-B27 starts to contribute to disease before it reaches the surface of the cell due to protein misfolding. Properly assembled HLA-B27 has a quaternary structure and contains 3 different components: 1 HLA-B27 heavy chain, beta-2-microglobulin and a peptide. This assembly takes place in the endoplasmic reticulum (ER) of the cell. Because the folding process of HLA-B27 is slower than that of other HLA-alleles, improperly folded HLA-B27 proteins are thought to accumulate in the ER. This misfolding process induces cellular stress, which leads to autophagy or another process termed the ER unfolded protein response (UPR), which can also activate the IL-23/IL-17 pathway. Evidence for the misfolding hypothesis in human disease has thus far been conflicting.[15]

5 | NEW BONE AND SYNDESMOPHYTE FORMATION

The most characteristic feature of AS is new bone formation leading to ankylosis of the sacroiliac joints and to syndesmophytes in the spine. Syndesmophytes are bony

growths in ligaments in the intervertebral joints and cause irreversible impairment of spinal mobility. New bone formation contributes to the disease burden independent of the inflammation-related pain and stiffness.[16] With new bone formation leading to ankylosis and syndesmophytes as the final result, the first step in joint remodelling in axSpA is loss of joint space due to cartilage loss, which is followed by cartilaginous fusion, and then bony fusion.[17] Molecular signalling pathways in bone development, such as dickkopf-1 (DKK-1), bone morphogenetic proteins (BMPs) and Wnt proteins have been studied in animal models of spondyloarthritis.[18] Relative inaccessibility of the spine limits studies in humans with most available data coming from post-mortem studies or from patient with long-standing AS undergoing spinal surgery. Furthermore, in patients, consistently replicated findings of serum biomarkers related to bone homoeostasis are scarce.[18]

Joint remodelling in axSpA including excess bone formation could be viewed as a straightforward repair mechanism following inflammation. If true, bone formation can be prevented by timely initiation of effective anti-inflammatory therapy. However, the observation that patients with AS treated with TNF-blockers did not differ compared to historic controls in radiographic progression over 2 years seemed to contradict this notion.[19] An alternative hypothesis agrees that inflammation comes first but suggests that areas of new bone formation in the spine could be a reactive attempt to increase spinal stability and could therefore occur at sites away from the inflammation. To truly counter excess bone formation, it would therefore be important to also decrease mechanical stress to the spine.[20] Given recent reports on more favourable outcome of long-term treatment with TNF-blockers on structural damage and perhaps promising reports on possible inhibition of structural damage with novel anti-IL-17 treatment, current opinion appears to shift to support the concept that timely, effective and sustained anti-inflammatory therapy will be most beneficial in preventing structural damage. Nevertheless, there is clear consensus on the need for further investigations.[21,22]

6 | MECHANICAL STRESS

Enthesitis is a hallmark of axSpA that sets it apart from other inflammatory rheumatic disease. Entheses are subjected to repetitive biomechanical stressing forces that are applied during movement. This suggests a link between biomechanical stress and axSpA. An enthesitis-based model for the pathogenesis of SpA has been proposed where interactions between biomechanical factors and the innate immune response may lead to disease.[3] Using limb unloading in animal models of SpA proof of concept studies have been done showing that mechanical strain may contribute both to entheseal inflammation and new bone formation in SpA.[23]

7 | LESSONS FROM TREATMENT

If a treatment against a particular proinflammatory mediator is effective in controlling disease symptoms, this may provide compelling evidence that that specific mediator plays a role in that disease. Nonsteroidal anti-inflammatory drugs (NSAIDs) were the first group of medications shown to be effective in treating axSpA. NSAIDs inhibit the activity of cyclooxygenase (COX) enzymes and thereby the synthesis of prostaglandins and thromboxanes. Genetic variation in the Prostaglandin E2 receptor 4 (EP4) gene which encodes a receptor for prostaglandin E2 has been associated with AS (Table 1).[24]

AxSpA patients with insufficient response to NSAIDs may respond well to targeted biologic agents that specifically inhibit tumour necrosis factor (TNF)-alpha or—in a more recent discovery—interleukin-17 (IL-17).[25] Interleukin-23 (IL-23 is a key stimulator of Th17 cells and blocking IL-23 using the IL-12/IL-23 blocker, ustekinumab has shown promising results in an open-label study in patients with AS.[26] However, a randomized controlled trial was reported to not have achieved the primary or major secondary endpoints (NCT02437162 posted September 29, 2017, at www. ClinicalTrials.gov). Based on genetic association data and animal studies IL-1 and IL-6 were promising targets but biological agents targeting these cytokines have not been effective in axSpA.[26] Interferon [IFN]-gamma is an important proinflammatory cytokine but data arguing for a role in axSpA are limited.

8 | INFECTION OR MICROBIOME?

In the arthritogenic peptide hypothesis, the association between HLA-B27 and axial SpA is explained by specific binding of microbial peptide similar to self-peptides to HLA-B27. The fact that reactive arthritis, a distinct form of spondyloarthritis, is triggered by genitourinary infections with Chlamydia trachomatis or by enteritis caused by bacteria, such as Shigella, Salmonella, Yersinia and Campylobacter species provides a solid background for this approach. But although Klebsiella or Chlamydia infections (Table 1) have been proposed as disease triggers by a few, a specific infection triggering axSpA is unproven.

Apart from potentially pathogenic microorganism, the human body (and in particular, the gut) contains a large community of commensal and symbiotic microorganisms collectively called the microbiota. The term microbiome is

used to refer to either to the collective genomes of these microorganisms or the microorganisms themselves.

Evidence that commensal gut bacteria are important in axSpA includes findings in animal models of SpA. In these models, rats and mice develop SpA-like clinical and pathologic features when housed in a regular laboratory environment, but not when raised in a germ-free environment.[27,28]

Data on changes in gut microbiota in SpA are emerging,[29] but it remains to be determined whether the microbiome of axSpA patient has a distinct signature and whether and how the microbiome influences disease. Nevertheless, there appears to be a general expectation that this is the case (Table 1).

9 | WHAT IS THE CELLULAR BASIS OF AXSPA?

In their theoretical framework for immunological disease, McGonagle and McDermott identify 2 extremes in immunological disease. On the 1 hand, pure autoimmune disease caused by recognition of self-antigens by the adaptive immune system and on the other hand, auto-inflammatory syndromes caused by disproportional activation of mainly innate cytokine pathways. Clear examples of the 2 extremes are found in rare monogenic disease (eg, autoimmune polyendocrine syndrome type 1 as an autoimmune disease and Familial Mediterranean fever and TNF receptor-associated periodic syndrome as auto-inflammatory diseases).[30]

However, according to the authors, axSpA with a clear and pronounced HLA association on the 1 hand and mechanical stress at entheseal sites as a possible eliciting factor for inflammation, on the other hand, shows a mixed pattern in the autoinflammatory/autoimmune continuum.

Indeed, although only immune cells are proposed to be involved in disease by multiple authors (Table 1: T cells including Th-17 cells, B cells, macrophages, NK cells) no clear consensus exists as to what part of the immune system and in particular, which immune cells are involved in disease.

A possible reason for this is that, although a wide spectrum of immune cells have been implicated in axSpA, few of these observations on the various immune cells in SpA have been replicated in other human studies. For instance, presence of autoantibodies has been investigated over the years, but has not been proven to be relevant in SpA. Recently, anti-CD74 autoantibodies have been described to be increased in patients with long-standing AS but their relevance in early disease has not been confirmed.[31]

Moreover, as most studies have been performed using samples from patients with long-standing disease often treated with potent immunomodulatory treatments for many years, it is often unclear if the findings are relevant to pathogenesis. Apart from effect of treatment, disease duration may be of particular relevance as innate and adaptive immune responses are intimately entangled, and chronic tissue inflammation could be accompanied by secondary T-cell and B-cell activation and vice versa.[32]

10 | DISCUSSION

Using a quantitative text analysis, review articles on the pathogenesis of axSpA published in the last 10 years were analysed for factors or mechanisms thought to be involved in the pathogenesis. With this information, we were able to provide an overview of the opinions and insight into the factors that are thought to be important by researchers in the field of axSpA. This method has clear limitations. The process of extracting statements about pathogenic factors and assigning keywords to these factors is subjective. Therefore, a second reviewer (FvG) reviewed a random selection of 33 articles. The most common pathogenic factors were assigned the same keyword, but there were differences between readers in identifying less common pathogenic factors. Moreover, the exact number of times a keyword was scored was seldom identical (Table S1).

Despite these limitations, our results indicate that there is broad consensus on a range of pathogenic factors involved in axSpA including the disease phase in which these factors are thought to have an effect. This appears to be particularly true for genetic risk factors, the role of the immune system and bone formation with most factors—with the exception of bone formation—thought to be involved in the initiation phase of the disease. Although relatively little is known on the relevance of possible changes in the human microbiome, among experts there is an expectation that this is the case.

Surprisingly, despite several published epidemiological observations, gender, smoking and physically demanding work were seldom mentioned as pathogenic factors in axSpA. The male predominance in severe AS has been known for a long time,[33] and smoking has been associated with progression of axSpA.[34] A possible explanation for the absence of these factors in our data is that it may be difficult to assign a specific disease mechanism to these factors and we only included factors for which a pathogenic mechanism was described. Finally, occupation is seldom mentioned in reviews. A possible reason for this is that occupation[35] is frequently used as a proxy for mechanical stress, in review articles this factor could be mentioned as mechanical stress directly instead of occupation.

Finally, although several types of immune cells have been implicated in axSpA there is little consensus on which cells drive disease. However, the progress in recent years including identification of multiple genetic risk factors, improvements in diagnosis, in particular, implementation of MRI for early diagnosis, and expanding therapeutic options including targeting the IL-17 and related cytokines, hold great promise for the future including a better understanding of the pathophysiology of axSpA.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: de Koning A, Schoones JW, van der Heijde D, van Gaalen FA. Pathophysiology of axial spondyloarthritis: Consensus and controversies. *Eur J Clin Invest*. 2018;48:e12913. https://doi.org/10.1111/eci.12913