Why location matters — site-specific factors in rheumatic diseases

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Abstract | Rheumatic diseases follow a characteristic anatomical pattern of joint and organ involvement. This Review explores three interconnected mechanisms that might be involved in the predilection of specific joints for developing specific forms of arthritis: site-specific local cell types that drive disease; systemic triggers that affect local cell types; and site-specific exogenous factors, such as focal mechanical stress, that activate cells locally. The embryonic development of limbs and joints is also relevant to the propensity of certain joints to develop arthritis. Additionally, location-specific homeostasis and disease occurs in skin and blood vessels, thereby extending the concept of site-specificity in human diseases beyond rheumatology. Acknowledging the importance of site-specific parameters increases the complexity of current disease paradigms and brings us closer to understanding why particular disease processes manifest at a particular location.

Specific anatomical patterns of joint and organ involvement characterize rheumatic diseases. Gout, reactive arthritis, ankylosing spondylitis and Behçet disease characteristically affect joints of the lower extremities and/or the spine. By contrast, patients with rheumatoid arthritis (RA), systemic lupus erythematosus, systemic sclerosis (SSc) or polymyositis typically develop arthritis in the small, distal joints of the hands and feet[1]. Similarly, the extra-articular organ involvement that can accompany rheumatic disease also shows a disease-specific pattern of anatomical distribution (FIG. 1). For instance, involvement of the eyes and the gut in addition to the spine is typical in patients with ankylosing spondylitis, and in psoriatic arthritis (PsA) the skin on the scalp, elbows, knees or lower back is characteristically involved.

The consistency with which these patterns appear suggests that the respective disease pathways are preferentially triggered at certain anatomic sites. A growing body of evidence supports the idea that the anatomical diversity of stromal cells not only guides local cellular specialization, tissue homeostasis and regeneration, but also contributes to location-specific disease development[2,3]. Molecules produced at the primary site of disease might also invoke pathological processes at susceptible secondary sites, inducing a disease-specific anatomical pattern of comorbidities.

In this Review, we discuss three potentially interconnected mechanisms that are involved in driving site-specific pathognomonic disease patterns. We also review studies in embryonic development that suggest a potential connection between the site-specific identities of tissue-resident cells involved in joint disease and embryonic development, as well as discussing epigenetic changes that occur during development. To conclude, we discuss the site-specific homeostatic functions of skin and responsiveness of the vasculature to inflammatory signals, demonstrating that the concept of location-specific characteristics and site-specificity in human diseases is broadly applicable beyond rheumatic diseases.

Site-specific factors in disease

Location is all-important in the development of rheumatic diseases. We propose three mechanisms to be involved in perpetuating disease at specific anatomic sites: site-specific local cells; systemic factors and the nervous system; and focal mechanical stress.

Local cells in joint disease. Synovial joints are specialized organs, built to meet the unique biomechanical and physiological needs of a given anatomic location. The structural elements of the synovial joint, such as the articular cartilage, synovial membrane (a delicate structure composed of one or two cell layers of synovial fibroblasts and tissue-resident macrophages), ligaments and menisci, support the specialized functions of individual joints.

An emerging body of data shows large differences in the transcriptomic and epigenomic profiles of synovial fibroblasts and articular cartilage from distinct joints[4–6]. This anatomical transcriptional diversity translates into joint-specific phenotypes of synovial fibroblasts[5]. For example, synovial fibroblasts from joints in the hands

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Key points

- Site-specific pathognomonic disease patterns are based on three interconnected mechanisms, namely site-specific local cells, systemic factors that affect particular anatomical sites and local mechanical factors
- Synovial fibroblasts and chondrocytes differ substantially between joints and might create location-specific joint microenvironments, rendering each joint more or less susceptible to different types of arthritis
- Evidence is emerging that local differences in joint innervation and vasculature might influence arthritis patterns; however, further studies are needed to strengthen these observations
- Local mechanical factors can aggravate joint disease, yet whether they trigger disease locally needs further clarification
- The overlap between site-specific embryonic traits and disease location suggests a role for embryonic pathways in the pathogenesis and occurrence of disease in joints, as well as in other organs

of patients with osteoarthritis (OA) and RA expressed larger amounts of matrix-degrading enzymes, such as collagenase 3, and displayed stronger proliferative and chemotactic properties than synovial fibroblasts from other joints[5]. These results might explain why the joints of the hand are primary targets of destruction in arthritis[7]. Additionally, synovial tissues from the hip joints of patients with RA or OA expressed higher levels of IL-6 when compared with synovial tissues from the knees of these patients[8]. The results of these studies suggest that each joint has a specific synovial microenvironment in health and disease. If this is true, then the local characteristics of the inflammatory response could define the susceptibility of a particular joint to developing disease. Similarly, it could be hypothesized that some types of arthritis present as oligoarthritides because fewer joint regions are susceptible to the triggering factor(s). It has been suggested that arthritis will present symmetrically when several joints in a certain region are affected[9]; therefore, the symmetric occurrence of arthritis might be a function of both the number of susceptible joint regions and the number of involved joints. The concept that joint microenvironments are susceptible or resistant to arthritis-specific pathogenic pathways could not only explain the anatomical patterns evident in arthritis, but might also reveal why arthritis can develop symmetrically or asymmetrically and manifest as either oligoarthritis or polyarthritis.

In contrast to other types of chronic arthritis, PsA affects a variety of joint regions with heterogeneous manifestations. The classic subgroups in PsA are distal interphalangeal (DIP) joint-predominant arthritis, asymmetrical oligoarticular arthritis, symmetrical polyarthritis, arthritis mutilans and predominant spondylitis, as described by Moll and Wright[10]. Conceivably, different pathogenic pathways could be operative in these different manifestations of PsA. For example, the symmetrical polyarthritis of the hands and feet that occurs predominantly in women might actually be a form of seronegative RA with concomitant skin psoriasis[11,12]. The occurrence of spondylitis, sacroiliitis, enthesitis, arthritis mutilans and dactylitis in patients with PsA are associated with different disease-risk genotypes, which code for various MHC class I receptors[13,14]. In particular, HLA-B27 is strongly associated with the involvement of entheses and the spine in patients with PsA and in other spondyloarthropathies, such as ankylosing spondylitis[13,15]. Additionally, HLA-B27-positive patients have an increased risk of eye involvement[16]. This pattern of disease manifestations at specific locations suggests that HLA-B27 expression is connected to pathogenic mechanisms that are specifically activated at these anatomic sites or that specifically activate these sites. HLA-B27 is thought to trigger an autoreactive T cell response by presenting self-peptides or by forming aberrant cell-surface complexes[17]. Other studies describe a high level of misfolded HLA-B27 molecules within cells, which induces endoplasmic reticulum (ER) stress[18]. The subsequent unfolded protein response and ER-associated degradation of HLA-B27 leads to increased production of IL-23 (REFS 17,18). Based on these studies, HLA-B27-driven processes could be supposed to be pronounced in resident cells of the spine, the entheses, the eye and the gut. For example, cell-type specific responses to ER stress have been described in different circumstances[19,20] and could potentially occur in the context of HLA-B27-associated spondyloarthropathies.

To understand completely whether and how local cells control joint-specific homeostasis and propensity for disease requires in depth analysis of healthy and diseased synovial tissue and cartilage from a variety of joints. Characterization of the synovial cellular infiltrate in different forms of arthritis should provide key insights into local pathological processes and uncover the exact, joint-specific function of cells that drive disease locally. An early study comparing the numbers of macrophages, synovial fibroblasts and T cells, and the level of IL-6 production between joints did not find any statistically significant differences between the synovia of small distal joints and knee joints in patients with RA[21]. However, more sophisticated approaches (such as single cell omics or multidimensional cytometry) can now be applied to decipher a possible role of specific local immune and stromal cells in arthritis.

Local response to systemic factors. Systemic factors substantially affect the physiology and pathology of joints. Synovial fluid is a transudate from blood plasma and, as the synovial membrane has no specific barrier function[22], most proteins that are present in the circulation can transfer to the synovial fluid. Joint-specific responses to systemic factors such as cytokines or autoantibodies could have a role in determining which joints develop arthritis. For example, high levels of IL-23 are released in response to misfolded HLA-B27 and the subsequent unfolded protein response[23]. IL-23 can potentially bind to local immune or stromal cells at particular anatomic sites; indeed, enthesitis was induced by IL-23 receptor^{+}CD3^{+}CD4^{-}CD8^{-} enthesis-resident cells in mice[24], lending support to the idea that local cells responding to systemic stimuli have a role in pathogenesis. Molecules produced at the primary disease site could then trigger disease at susceptible secondary sites.

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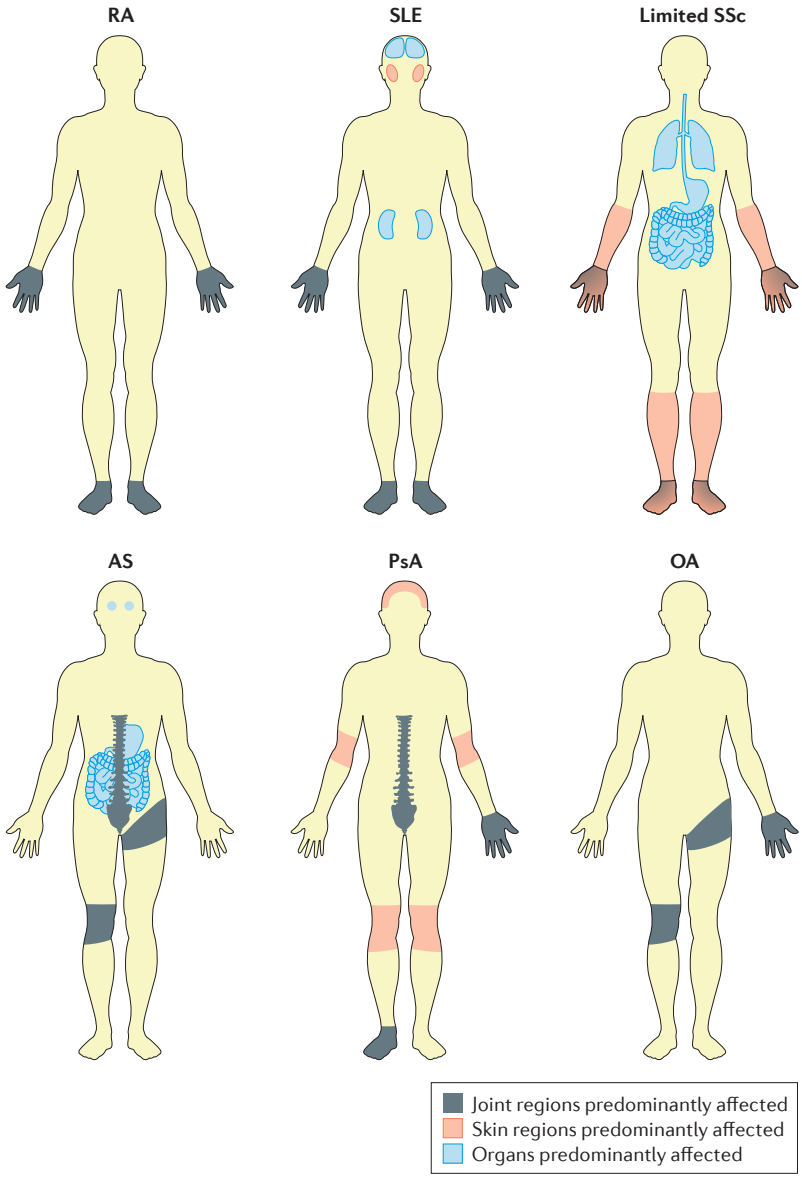

Figure 1 | **Patterns of joint and organ involvement in rheumatic disease.** Even though rheumatic diseases can present with variable symptoms in individual patients, characteristic patterns of joint and organ involvement are distinguishable between rheumatic diseases. AS, ankylosing spondylitis; OA, osteoarthritis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

The synovium is a highly vascularized tissue that is innervated by myelinated and unmyelinated nerve fibres. Studies in the K/B×N serum transfer model of murine arthritis showed an increased capacity for leakage of macromolecules, such as immune complexes, from the vasculature into the joints of the distal extremities[25]. These 'leaky blood vessels' could explain the characteristic distal pattern of arthritis (wrists, ankles, hind paws and front paws) observed in the K/B×N serum transfer model[26,27]. Unilateral transection of the femoral and sciatic nerves in these mice inhibited the leakage of macromolecules into joints, thereby protecting the hind paws from the development of arthritis[25]. The endothelial cells of denervated hind paws in these mice displayed altered expression of a number of genes involved in vascular leakage and transendothelial cell migration[25], suggesting that the nervous system might control the response to inflammation of the joint microvasculature during the course of arthritis. Whether similar mechanisms are operative in arthritis in humans remains speculative; nevertheless, denervation was shown to protect the joints of paretic or paralytic extremities in humans from the development of arthritis, particularly RA[28–33]. The specific characteristics of the nerve fibres that influenced the distal vasculature in the K/B×N serum transfer model of arthritis were not identified in the studies discussed. Similarly, which of the arms of the nervous system (motor, sensory or autonomous) are involved in the remission of arthritis in paretic and paralytic extremities in humans remains unknown.

The nervous system has a role in modulating the inflammatory response in arthritis, particularly in conferring the symmetrical pattern of joint involvement. Contralateral joint inflammation is inhibited by pharmaceutical or surgical nerve blockade in various animal models[34]. Both spinal stimulation and central stimulation of contralateral neurons have been suggested as drivers of antidromic neuronal activity, with sensory and sympathetic nerve fibres thought to be involved[35]. However, it is likely that an integrated response of several types of neurons is critical for the regulation of joint inflammation. Joints have independent innervation, so the ratio of sympathetic and sensory nerve fibres can vary between joints. The quantity and quality of joint nerve fibres might have a role in determining the propensity of a joint to develop arthritis[36]. Indeed, the number of substance P-producing nerve fibres was higher in ankles compared with knee joints in rats[36], and in equine metacarpophalangeal joints compared with carpal joints[37]. Exploring the site-specific aspects of joint innervation and the neuroregulation of the vasculature at arthritis-susceptible and arthritis-resistant anatomic sites in humans and in animal models could further delineate the role of the nervous system in the anatomical patterning of arthritis.

Site-specific mechanical factors. Different anatomic locations expose joints to different types of mechanical stress. During grasping and holding motions that utilize all five fingers, the majority of mechanical strain is exerted on the index and middle fingers (digits II and III)[38]. Concordantly, joint swelling and tenderness in OA, PsA and RA are most severe in digits II and III[39,40], and osteophytes are frequent in the joints of these two digits in PsA and OA[39,41]. These observations illustrate that local mechanical strain can aggravate joint disease independently of underlying disease mechanisms. Additionally, mechanical strain might be able to trigger arthritis; the incidence of RA and gout are connected to physical trauma[42–44]. A pathological role for mechanical stress in the development of enthesitis in patients with spondyloarthropathies[45] and arthritis in the DIP joints of patients with PsA[46] is largely accepted. Although lifting heavy loads has been linked to the development

Contralateral joint inflammation
Inflammation in joints on one side of the body resulting from inflammation induced in joints on the other side of the body.

Antidromic neuronal activity
An impulse that runs along the axon towards the cell body in the opposite direction to a normal signal.

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Proximal–distal body axis
The body axis running from the parts of the limbs that are nearest to the trunk of the body through to the parts that are furthest away, also called the medial–lateral axis.

Anterior–posterior body axis
The body axis running from the head to the feet; in humans corresponding to the axis running from the superior (or upper) body parts to the inferior (or lower) body parts.

of PsA, no particular pattern of joint involvement was observed[47]. Altered local forces caused by post-traumatic or congenital joint malalignment has been associated with human OA and reproduced in various animal models[48]. By contrast, the proposed connection between local joint biomechanics and arthritis development in the small joints of the hand remains to be formally demonstrated. Some studies have shown a connection between heavy or repetitive occupational use of the hands and development of hand OA[49,50]; however, other studies did not confirm these findings[51,52]. Detailed analysis of OA in various joints of the hand revealed a high prevalence of OA in digits IV and V, a propensity that is difficult to explain by mechanical strain alone[52].

Frequent colocalization of cartilage damage and monosodium urate (MSU) crystal deposition suggests that the development of OA and gout might be interdependent[53]. High levels of cartilage breakdown-products affect the solubility of urate in OA joints, thereby supporting the formation of MSU crystals[54–56]. Forty years ago, Simkin[57] proposed a model in which mechanical stress or physical trauma can lead to synovial effusion in the first metatarsophalangeal (MTP I) joints of patients with OA, which is resorbed during the night. The nocturnal resorption of the effusion increases the concentration of urate in the synovial fluid, which subsequently leads to the formation of MSU crystals, eliciting a gouty attack. Low temperatures and previous physical trauma might further promote crystal formation in the MTP I joint[58,59]. This model elegantly explains why gouty attacks predominantly start during the night but does not clarify why gout characteristically affects the MTP I joint. The exposed position of the MTP I joint in the foot makes it susceptible to trauma and changes in temperature, and this joint frequently becomes osteoarthritic as well as gouty, yet DIP and proximal interphalangeal (PIP) joints of the hands, which are similarly exposed to trauma and temperature conditions, are equally susceptible to OA but infrequently develop gout[60]. Therefore, in addition to exposure to trauma and local temperature conditions and an increased prevalence of OA, other factors must have a role in determining the susceptibility of the MTP I joint to gout.

Overall, mechanical strain can aggravate arthritis and there is a proven pathogenetic connection between some forms of OA and focal mechanical strain or injury[61]. In other types of arthritis, however, a pathogenetic relationship between local mechanical strain and the site-specificity of disease remains to be established. An increased knowledge of local tissue physiology might provide key insights into the local effects of systemic and mechanical factors in the site-specificity of arthritis development. In the following sections, we discuss the specific roles of embryonic joint and limb development (and the accompanying epigenetic architecture) in shaping the local features of joints that might predispose them to disease.

Developmental factors in disease

Different types of arthritis present with characteristic patterns of joint involvement along the embryonically established proximal–distal body axis and anterior–posterior body axis (FIG. 2a), as seen in the prevalence of distinct types of arthritis in the anterior versus posterior and distal versus proximal extremities. Distal extremities are particularly vulnerable to destructive arthritis, with different types of arthritis affecting joints along the proximal–distal and anterior–posterior axes of the hands and feet (FIG. 2b). OA characteristically affects the first carpometacarpal (anterior) and DIP joints

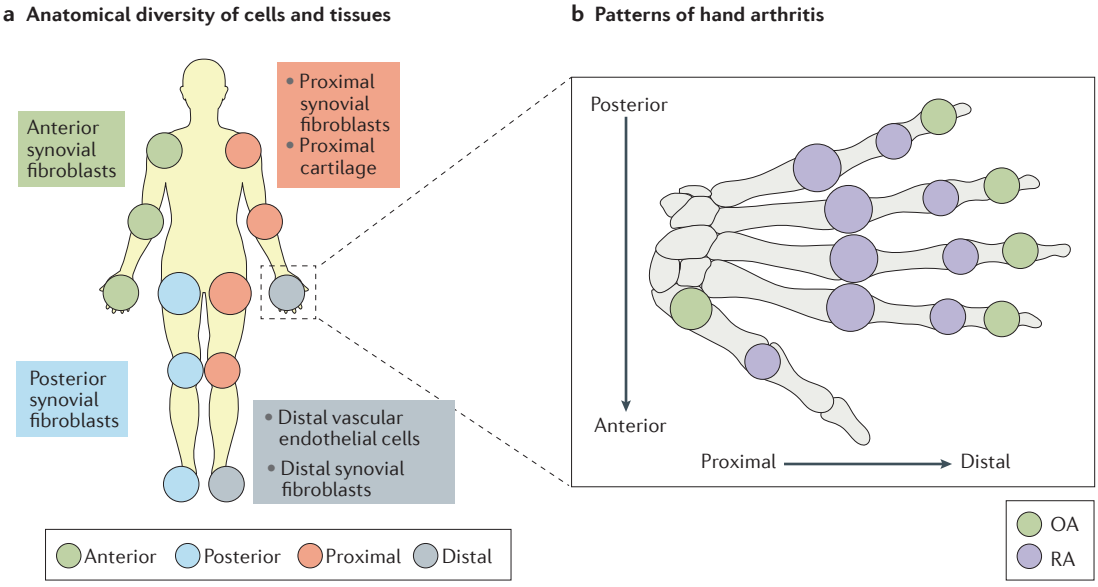

Figure 2 | **Anatomical diversity in joints and patterns of joint involvement in rheumatic disease. a** | Synovial fibroblasts, cartilage and vasculature differ between anatomic locations along the body axes. **b** | Joints in the hands commonly involved in rheumatoid arthritis (RA) and osteoarthritis (OA).

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(not typically affected in RA), whereas the wrists, metacarpophalangeal joints and PIP joints of the posterior digits (II–V) typically develop RA, and gouty arthritis characteristically affects the MTP I joint. The overlap of arthritis patterns and embryonic development patterns indicates a possible role for embryonic factors in disease development. The studies summarized in this section highlight developmental processes that might contribute to the anatomical diversity of joints affected by arthritis.

The spatial and temporal expression of key developmental genes such as the homeobox (HOX) family genes, sonic hedgehog (*SHH*) and the T-box (TBX) family of transcription factors tightly control the correct establishment of the body axes and accurate morphogenesis of the skeleton in the limbs[62–65]. During embryonic development, posterior body parts express genes encoded in the 5′ region of the HOXC gene cluster[66]. *HOXA9-HOXA13* and *HOXD9-HOXD13* (encoded at the 5′ end of the HOXA and HOXD gene clusters, respectively) are expressed in a specific proximal–distal pattern that defines the identity of the skeletal elements of the limbs — the stylopod (humerus and femur), the zeugopod (radius, ulna, tibia and fibula) and the autopod (hands and feet)[67] (FIG. 3a). In the autopod, the expression of specific HOXD family genes varies between the digits, determining the identities of the digits along the anterior–posterior axis[65] (FIG. 3b). *Hoxd11-Hoxd13* and *Hoxa13* determine the identity, size and number of digits in mice[68]. A stepwise reduction of *Hoxd11-Hoxd13* and *Hoxa13* gene dosage leads to digit anomalies ranging from polydactyly to oligodactyly and adactyly[68]. *Hoxd11*$^{-/-}$*Hoxd12*$^{-/-}$*Hoxd13*$^{-/-}$ triple-knockout mice, *Hoxd13*$^{-/-}$*Hoxa13*$^{+/-}$ mice and *spdh/spdh* mice (mice with a synpolydactyly homologue mutation consisting of a polyalanine expansion in *Hoxd13*) have metacarpal bones that have transformed into carpal-like bones (long bones with joints at the ends that become ovoid bones surrounded by joints)[69]. Accordingly, a homozygous *HOXD13* +9 Ala expansion mutation showed similar anomalies in shape and ossification of metacarpal bones in humans[69,70]. Heterozygous mutations in *HOXA13*, mutations in *HOXD13* and mutations in the noncoding regulatory region of *SHH* also cause various anomalies in digit size and/or number in humans[71,72].

Adult cells and tissues, including skin fibroblasts[73–75], vascular smooth muscle cells[76], cartilage[2], bone[3], colon[77] and adipose tissue depots[78] retain key features of their embryonic gene signatures. A 2017 study[5] showed that the adult human synovium and synovial fibroblasts also retain principal aspects of site-specific expression of embryonic HOX family and other developmental limb-patterning genes. Synovial fibroblasts from joints in the hands and feet (distal) selectively expressed genes located in the 5′ tip of the HOXA and HOXD gene cluster, such as *HOXA13*, whereas synovial fibroblasts from joints in the posterior extremities specifically transcribed genes encoded in the 5′ region of the HOXC gene cluster[5]. The long noncoding RNA HOTAIR (HOX transcript antisense RNA), encoded in the HOXC gene cluster, was exclusively expressed in synovial fibroblasts from the joints of the posterior extremities[5]. Silencing of HOTAIR in knee synovial fibroblasts led to increased constitutive and TNF-induced expression of interstitial collagenase (also known as MMP1), indicating that HOTAIR can control the site-specific and cytokine-driven matrix-destructive properties of synovial fibroblasts[5]. These observations illustrate how developmental genes can control the activation of arthritis-relevant pathways in the

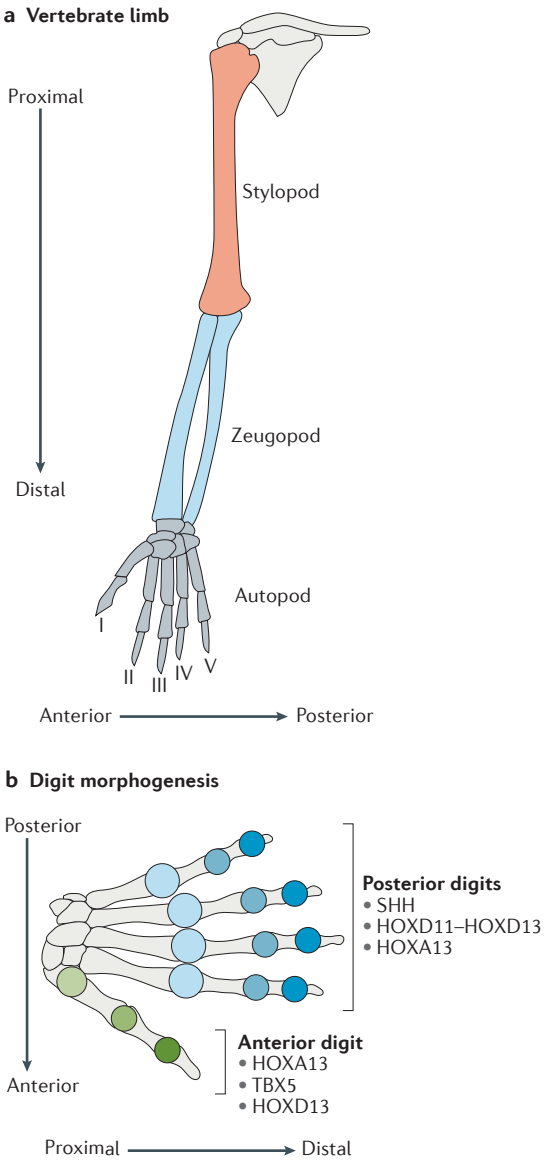

Figure 3 | **Development of limbs and digits in vertebrates. a** | The skeletal domains of a vertebrate limb along the proximal–distal (stylopod to autopod) and anterior–posterior (digits I–V) limb axes. **b** | Different molecular factors are involved in anterior and posterior digit morphogenesis, controlling digit number and size. HOXA13, homeobox protein Hox-A13; HOXD11, homeobox protein Hox-D11; HOXD13, homeobox protein Hox-D13; SHH, sonic hedgehog; TBX5, T-box transcription factor TBX5.

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synovium, thereby guiding the development of arthritis-specific patterns of joint involvement along the principal developmental body axes.

Embryonic development of joints. Early in skeletal development the cartilaginous skeleton is uninterrupted; the formation of joints begins with the emergence of a compact layer of mesenchymal tissue (the interzone) at the site of each future joint, interrupting the continuity of the skeletal template[79,80] (FIG. 4a). After the specification of joint sites, physical separation of the adjacent cartilaginous elements and formation of the synovial cavity (joint cavitation) occur, followed by the formation of joint structures such as the articular cartilage, synovial membrane, ligaments and menisci[79,80]. All these joint structures originate from cells in the interzone that express growth/differentiation factor 5 (GDF5), a member of the bone morphogenetic protein (BMP) family[79,81] (FIG. 4).

Joints develop through the continuous influx of GDF5-expressing cells into the interzone[81]. A highly dynamic spatiotemporal pattern of GDF5 expression guides the formation of the different joint structures; both the onset and the duration of GDF5 expression seem to be crucial in this process[81]. Therefore, the spatiotemporal dynamics of GDF5 expression in the interzone could instruct the divergence of cells into different lineages to form the distinct joint compartments (FIG. 4b). Despite the widespread expression of GDF5 in joint-forming tissues throughout the skeleton, a lack of GDF5 in humans and mice affects only a subset of joints, most notably the joints of the autopod[82], whereas single nucleotide polymorphisms (SNPs) in *GDF5* specifically predispose individuals to knee OA[83]. These site-specific effects of GDF5 might result from a strong interconnectivity between members of the BMP family, environmental stimuli and other developmental pathways[84].

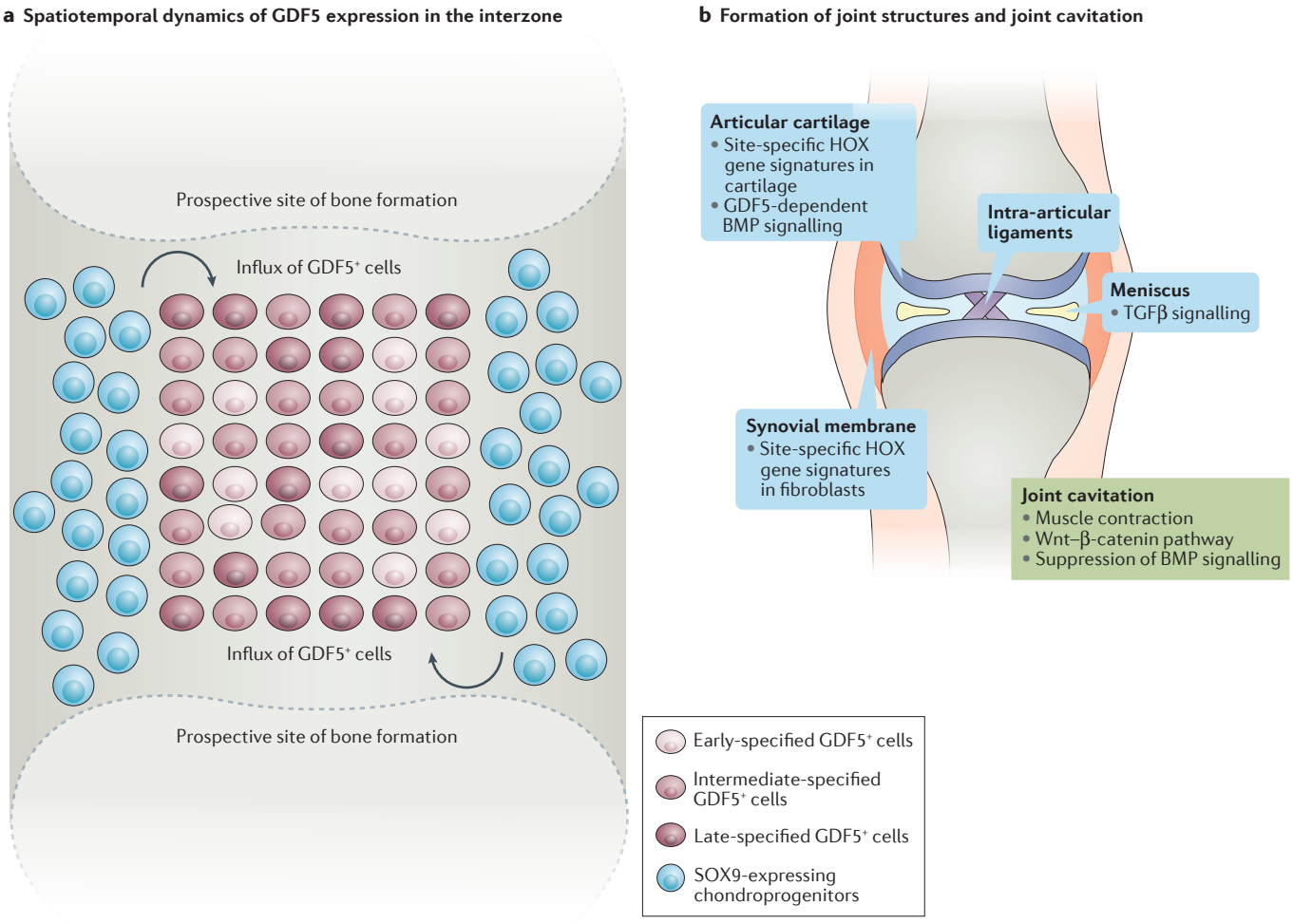

Figure 4 | **Morphogenesis of synovial joints. a** | The first sign of future joint formation is the emergence of a compact layer of mesenchymal tissues, known as the interzone. The interzone is specified by the induction of growth/differentiation factor 5 (GDF5) expression and suppression of collagen α1(II) chain expression in interzone cells. Joints form through a continous influx of GDF5-expressing cells in the interzone, which originate from transcription factor SOX9-expressing chondroprogenitors. **b** | Joint structures, including articular cartilage, synovial membrane, menisci and intraarticular ligaments originate from GDF5-specified joint progenitor cells. The spatiotemporal dynamics of GDF5 expression in the interzone guides lineage divergence of the recruited interzone cells to form the different joint tissues. Other developmental factors, such as bone morphogenetic protein (BMP), homeobox (HOX) genes, the Wnt–β-catenin pathway and transforming growth factor-β (TGFβ) contribute to the morphogenesis of articular structures and guide joint cavitation in a site-specific manner.

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Environmental cues that activate core morphogenetic signalling pathways at particular sites help to configure the site-specific features of joint morphogenesis. For example, fetal movements are required for normal joint formation[85]. A lack of limb musculature (as in muscleless mice) or complete muscle paralysis (as in *mdg* mutant mice) during development results in the specific loss of certain joints (elbow, shoulder, hip, talocalcaneal, specific midcarpal joints and intervertebral joints of the cervical and lumbar spine, the latter in *mdg* mutant mice only), while other joints such as knees and finger joints remain intact[86]. Although joint progenitor cells are specified by the presence of GDF5 in these mice, these cells fail to maintain joint identity in the absence of contracting musculature and 'erroneously' differentiate into chondrocytes, precluding joint cavitation and leading to joint fusion[86]. The Wnt–β-catenin pathway is required for maintaining the commitment of joint progenitor cells to a joint-cell fate and for suppressing chondrogenic differentiation[87,88]. The sites of prospective elbows in muscleless and *mdg* mutant mice have reduced β-catenin activity, but these mice have normal β-catenin activity at presumptive knee and finger joints[86]. β-Catenin signalling seems to be differentially regulated in different joints, with muscle contraction controlling β-catenin activity and joint formation in only a subset of anatomic sites (FIG. 4b). Tissue surrounding the developing elbows in mice is highly enriched in transcripts involved in muscle specification and differentiation[80]. By contrast, knee-forming tissues are enriched in *Hoxc9* and *Hoxc10*, as well as transcripts involved in Wnt signalling and members of the transforming growth factor-β (TGFβ) superfamily such as TGFβ and BMP[80]. TGFβ guides knee morphogenesis and meniscus formation[79,80] whereas different members of the BMP family are crucial in the development of the axial skeleton, the limbs and the digits[84]. Regionalization of the activity of BMP signalling within the interzone — suppression in the centre and GDF5-induced activation in the outermost parts — seems to be important for proper joint cavitation and articular cartilage formation[84] (FIG. 4b). Inherited defects in BMP signalling result in errors in digit size and joint fusions, particularly in the autopod[84].

Developmental pathways in OA. The hips, the knees and the small joints of the hands (PIP and DIP joints) characteristically develop OA, although the disease manifests differently in these joints, and can even differ between the joints of the hands, manifesting as different phenotypes (erosive OA, nodal interphalangeal OA and thumb base OA). There is ample evidence for the role of developmental pathways in the pathogenesis of OA[89]. Briefly, rs143383, a SNP in the 5′ UTR-coding region of *GDF5* prominently increases the risk of developing knee OA, and SNPs in *ANP32*, which encodes acidic leucine-rich nuclear phosphoprotein 32 family member A, a member of the Wnt signalling pathway, are associated with the risk of hip OA in women[83,90]. These results suggest that polymorphisms in genes encoding proteins in key developmental pathways might predispose an individual to joint-specific forms of OA. The large number of embryonic signalling pathways that are involved in the pathogenesis of OA and are upregulated at specific sites during embryonic development, such as the Wnt–β-catenin, BMP and TGFβ pathways[91], strongly suggests that these pathways are involved in the site-specific development of OA, as well as the severity of disease.

Epigenetics in site-specificity

Epigenetic mechanisms such as histone modification and DNA methylation have a central role in establishing site-specific patterns of gene expression during embryogenesis[92,93]. In adult skin fibroblasts, synovial fibroblasts and chondrocytes from various anatomic locations, differences in DNA methylation and histone modifications at HOX family gene loci exist[4–6,8]. Therefore, epigenetic mechanisms could control the faithful maintenance of embryonic gene expression patterns in adult cells throughout their lifetime.

Several studies have analyzed and compared the DNA methylation profiles of knee and hip cartilage from patients with OA and healthy individuals[4,6,94]. Notably, these studies showed only a small amount of overlap in differentially methylated loci between knee OA and hip OA, underlining the different pathogenic pathways that are active in OA at these two sites. The methylated loci that differed between these joint locations were consistently enriched for genes involved in limb development, such as HOX family genes.

Studies in embryonic mice show that *Tbx5* is expressed in anterior body parts and is required to ensure forelimb symmetry in mice[95] (FIG. 3b). Mutations in *TBX5* cause Holt-Oram syndrome in humans, which is characterized by skeletal deformities in the anterior extremities that are pronounced on the left-hand side[95]. Similar to HOX family genes, the embryonically-established, site-specific expression of *TBX5* is maintained in adult synovial fibroblasts[5]. Interestingly, epigenetic modifications that normally silence *TBX5* in synovial fibroblasts in posterior body parts are altered in knee synovial fibroblasts from patients with RA, and TBX5 is aberrantly expressed in these cells[96]. TBX5 regulates the expression of chemokines such as IL-8 and stromal cell-derived factor 1 (also known as CXCL12) in synovial fibroblasts, indicating that a loss of epigenetic imprinting of embryonic genes might have an influence on development of RA[96].

The effects of the SNP rs143383 in *GDF5* are stronger and more consistent in the development of knee OA compared with hip or hand OA[83]. The risk allele (T) of rs143383 leads to diminished transcription of *GDF5* by influencing the upstream binding of repressive transcriptional regulators[97]. *In vitro*, this effect was potentiated when the DNA region encoding the 5′ UTR of *GDF5* was demethylated[98]. The region surrounding rs143383 was hypomethylated in knee cartilage compared with hip cartilage[98], suggesting that differences in DNA methylation between hip and knee joints could underlie the joint-specific effects of rs143383 in OA.

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These observations further substantiate the role of epigenetics, not only in site-specific synovial gene expression, but also in driving pathological processes locally. Acknowledging that most of the OA-risk SNPs identified to date are specific for a joint region, future studies in OA and other types of joint disease should focus on integrating genomic data with joint-specific epigenetic and transcriptional profiles[99].

Site-specificity outside of the joint

The location-specific expression of embryonic genes in adult cells not only has a key role in site-specific homeostatic functions, but is also emerging as an important factor for site-specific disease development in organs and pathologies external to the joints.

Skin. Skin is an anatomically highly specialized tissue, as exemplified by the location-specific occurrence of body hair, sweat glands, glabrous skin and pigmentation, as well as the site-specific susceptibility to diseases such as psoriasis, scleroderma, acne and keloids. Skin fibroblasts from different sites of the body display morphological and functional heterogeneity attributable to their origins in different germ layers[100], to their anatomical diversity[73] and to intradermal sub-specialization[100]. Distal-specific expression of *HOXA13* and concomitant homeobox protein Hox-A13 (HOXA13)-dependent regulation of protein Wnt5A in plantar skin fibroblasts is central to the induction of palmoplantar-specific expression of keratin type I cytoskeletal 9 (CK9), underlining the role of HOX family genes in site-specific epidermal differentiation[101]. Non-palmoplantar human keratinocytes start to express CK9 when co-cultured with palmoplantar skin fibroblasts[102]. Similarly, non-palmoplantar epidermis adopts a CK9-positive palmoplantar epidermal phenotype when grafted onto wounds on the soles of the feet in humans[102]. These studies substantiate a key role for local fibroblast signals in controlling site-specific skin repair and differentiation.

It is largely unknown how the positional identity of skin fibroblasts (and potentially other local cell types) confers site-specific susceptibility to skin diseases. SSc affects both the skin and the joints of the distal extremities, which could be connected to the common expression of embryonic genes such as *HOXA13* at these sites. However, further studies are required to unravel the specific contributions of local cells, distally acting systemic factors and distal-specific mechanical factors in shaping distal skin and joint manifestations in SSc. Another disease characterized by a specific anatomical pattern of skin involvement is psoriasis. In particular, psoriasis of the scalp and nails predisposes to PsA[103], suggesting that specific pathways that are active in scalp and nail psoriasis might lead to subsequent involvement of the joints[46]. Alternatively, the skin of the scalp, the nails and the joints might share susceptibility to a systemic trigger that invokes pathogenic processes at all these sites. The Koebner response is one example of how local mechanical stress can trigger disease development. This phenomenon might also contribute to the development of joint disease in patients with PsA[104,105].

Koebner response
A disturbed reaction to trauma and mechanical stress that leads to skin lesions in patients with psoriasis.

Blood vessels. Despite the presence of systemic risk factors such as arterial hypertension, diabetes mellitus or autoimmune responses, blood vessels display striking regional differences in their susceptibility or resistance to specific vascular pathologies (such as atherosclerosis, aortic aneurysm or vasculitis)[106]. Differences in regional haemodynamics and vessel wall structure have long been considered to be responsible for the characteristic regionalization of aortic atherosclerosis and aneurysms. However, accumulating evidence suggests that the embryonically established anatomic diversity of the aortic wall could have an equally important role[107].

Vascular smooth muscle cells of distinct embryonic origins are phenotypically diverse, displaying different potential for growth and responsiveness to cytokines such as TGFβ[108]. Smooth muscle cells in the aortic arch originate from the neural crest, whereas smooth muscle cells in the descending aorta derive from somatic mesoderm. Atherosclerosis-prone murine aortic arch *in vivo* and cultured murine smooth muscle cells from the aortic arch express lower levels of HOX gene paralogues 6–10 and have higher activation of the transcription factor NF-κB compared with atherosclerosis-resistant descending aorta and descending aorta-derived smooth muscle cells[76]. Overexpression of *Hoxa9* limited NF-κB signalling in rat embryonic aortic E19P cells and in murine smooth muscle cells from the aortic arch. In turn, overexpression of NF-κB in E19P cells or murine thoracic aorta-derived smooth muscle cells or stimulation of E19P cells with TNF resulted in the suppression of *Hoxa9* (REF. 76). These results suggest that site-specific *Hoxa9* expression in aortic smooth muscle cells controls the segment-specific proinflammatory responsiveness of the aorta, contributing to the characteristic regionalization of aortic atherosclerosis.

Similar to smooth muscle cells, endothelial cells from different organs and different areas of the vasculature show extensive molecular and phenotypic heterogeneity, further enhancing the regional diversity of the vasculature[109,110]. Differential expression of HOX family genes defines the tissue-specific and organ-specific origins of endothelial cells[110]. Site-specific expression of the microRNA miR-10a (encoded in the HOXB gene cluster) might contribute to the regional susceptibility of the aorta to atherosclerosis[111]. Atherosclerosis-susceptible endothelium of the porcine aortic arch and the aorto-renal vascular branches contain lower amounts of miR-10a than the atherosclerosis-protected descending aorta. Silencing of miR-10a in cultured human aortic endothelial cells increases the nuclear translocation of NF-κB and enhances the expression of proinflammatory cytokines and adhesion molecules[111], indicating a prominent role for miR-10a in configuring the regional proinflammatory nature and susceptibility of the aortic endothelium to atherosclerosis.

In line with these results, the differential segmental responsiveness of the arterial wall to systemic cytokines might contribute to the increased incidence of atherosclerosis in patients with rheumatic diseases such as RA[112]. Likewise, embryonic features and other

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segment-specific characteristics of the vessel wall could underlie the site-specific vulnerability of vessels to developing different types of vasculitis[106].

Conclusions

Genome-wide studies of genetics, epigenetics and coding and noncoding transcripts have substantially increased our understanding of pathological processes in joints affected by rheumatic diseases, but it remains a challenge to combine these datasets and approaches to get a clear picture of the spatiotemporal activation of the pathways involved. Decoding the characteristic features and embryonic traits of affected and protected sites might provide new clues about causal pathogenic mechanisms and therapeutic opportunities. Knowledge of pathogenic mechanisms has to be integrated with known anatomical characteristics of affected sites to better understand the causes and the consequences of arthritis-specific patterns of joint and organ involvement. Disease activity scores might be an adequate tool to assess response to treatment, but for practical reasons these scores often do not include all affected sites. The 28-joint disease activity score (DAS28), for instance, does not include the ankle, MTP or PIP joints in the feet, and studies correlating inflammatory factors and/or treatment response with DAS28 scores might miss important changes in disease activity at these locations[113]. Furthermore, information on the patterns of joint involvement in animal models of arthritis is scarce. Although most models have affected distal joints, disease involvement in other joints is not usually communicated. Including information on patterns of joint involvement as an integral part of *in vivo* data reporting, and stringent selection and reporting of anatomical sampling locations in *in vitro* studies should help to deepen our current understanding of site-specific vulnerability to arthritis and the local factors involved.

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