Overview

Jessica Bertrand and Jan Hubert

Anatomy and Physiology of Joints

Joints Classification

Joints are locations at which two or more bones come together. They are often constructed to allow movement and provide mechanical support. Joints can be classified functionally based on the amount of movement allowed: "synarthroses" are immovable, "amphiarthroses" are slightly movable, and "diarthroses" are freely movable.

Joints can also be classified structurally, describing how the bones connect to each other, as fibrous, cartilaginous, and synovial. Synarthroses are fibrous joints that connect bones without allowing any movement and are found, for example, in the skull and pelvis and at the union of the spinous processes and vertebrae. In cartilaginous joints (amphiarthroses), the bones are attached by cartilage, and they allow for only a little movement, such as in the spine or ribs. Synovial joints, also called diarthroses, are of crucial importance for the skeletal function, as they permit a wider range of movement. The ends of the opposing skeletal elements in synovial joints are covered with articular cartilage. The spaces between the bones in synovial joints are filled with synovial fluid, which helps to lubricate and protect the cartilage and nourishes the tissues. The joint is surrounded by the synovial membrane and held together by the fibrous joint capsule (that insulates the joints from surrounding tissues) and ligaments (that hold the skeletal elements in place) [1].

Synovial joints can be distinguished again into six different types depending on the mobility and type of movement they allow for: gliding, hinge, pivot, condyloid, saddle, "ball and socket," and compound joints.

The following passages will describe the different structures of synovial joints, with special emphasis on biochemical processes that play a role during joint homeostasis.

Joint Formation

A process called endochondral ossification mediates the formation of long bones and thereby the formation of articular joints in arms and legs (see chapter "Overview" under part "Teeth and bones"). During the differentiation of mesenchymal cells into chondrocytes, the expression pattern of extracellular matrix proteins changes. While the expression of collagen I decreases, chondrocytes start producing collagens II, IX, and XI as well as proteoglycans like aggrecan, link protein, and matrix Gla protein [2]. At the ends of

J. Bertrand (✉)
Institute of Experimental Musculoskeletal Medicine IEMM, University Hospital Muenster, Domagkstrasse 3, Muenster 48149, Germany
e-mail: bertrand@uni-muenster.de

J. Hubert
Klinik und Poliklinik für Orthopädie, Universitätsklinikum Hamburg-Eppendorf, Martinistrasse 52, Hamburg 20246, Germany
e-mail: j.hubert@uke.de

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the bones, this composition of cartilage matrix is retained, and the chondrocytes do not differentiate any further and form the articular cartilage.

In the bone-forming parts of the embryonic cartilage, chondrocytes differentiate further and become hypertrophic. As part of their hypertrophic differentiation, they start to express collagen X. With beginning bone formation, cartilage undergoes vascularization [2, 3], and the extracellular matrix gets mineralized. Subsequently, a continuous cycle of bone remodeling starts, driven by resorbing osteoclasts and bone-forming osteoblasts (see chapter "Overview" under part "Teeth and bones").

During osteoarthritis (see chapter "Osteoarthritis"), however, articular chondrocytes also undergo prehypertrophic to hypertrophic maturation. This differentiation is accompanied by an increase in expression of certain marker genes, such as alkaline phosphatase [4] and collagen X [5], with subsequent mineralization of the diseased cartilage [5].

Joint-Specific Pathways and Processes

Bone

The aforementioned balance between bone formation and resorption is regulated by macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor-κB ligand (RANKL) [6, 7]. M-CSF is constitutively expressed in osteoblasts and binds to receptors on monocytes, macrophages, and osteoclasts, thereby inducing osteoclast maturation and differentiation. RANKL, however, is mainly expressed in osteoblasts in response to factors that stimulate bone resorption, such as parathyroid hormone and calcitriol. RANKL binds to its receptor on osteoclast precursors, initiating their maturation. Bone resorption induced by RANKL can be blocked by osteoprotegerin (OPG), which is also secreted by osteoblasts and osteogenic stromal stem cells (see chapter "Overview" under part "Teeth and bones").

The Wnt signaling pathways (canonical and noncanonical) play a central role in bone remodeling in both physiological and pathological conditions. Canonical Wnt signaling promotes differentiation of osteoblast precursor cells (Fig. 1) [8, 9]. Additionally, this pathway suppresses bone resorption by shifting the RANKL/OPG ratio towards OPG in mature osteoblasts [10]. However, the activation of the noncanonical pathway enhances the RANKL-induced osteoclast formation [11].

Cartilage

Cartilage is a flexible form of connective tissue. The predominant form is hyaline cartilage, named after its glassy, translucent appearance. It is commonly associated with the skeletal system, as it covers the bones and represents the articular cartilage in joints. It is also found between the ribs and the sternum or breastplate, in the trachea and bronchi of the lungs, in the ear, and in the larynx or voice box. Macroscopically, articular cartilage can be divided into the superficial zone, the transitional zone, the radial zone, and the calcified cartilage zone, where the cartilage interfaces with the bone (Fig. 1) [12]. These zones are characterized by a distinct organization of the collagen network, as well as by differences in the amounts and types of proteoglycans. Type II collagen is the principal molecular component in healthy articular cartilage, but collagens III, VI, IX–XII, and XIV all contribute in smaller amounts to the mature matrix [13–15], whereas the collagens IX, X, and XI are specific for cartilage tissue. The main proteoglycan is aggrecan. It is important for the biomechanical properties of articular cartilage because it builds a hydrated gel structure due to its interaction with hyaluronan and link protein. Due to these properties of aggrecan, the cartilage is a rigid and reversibly deformable tissue that has the ability to resist compression.

The only cells found in cartilage are chondrocytes. In adult cartilage, the chondrocytes remain resting in a non-proliferating state, but display moderate metabolic activity and the ability to maintain the surrounding matrix.

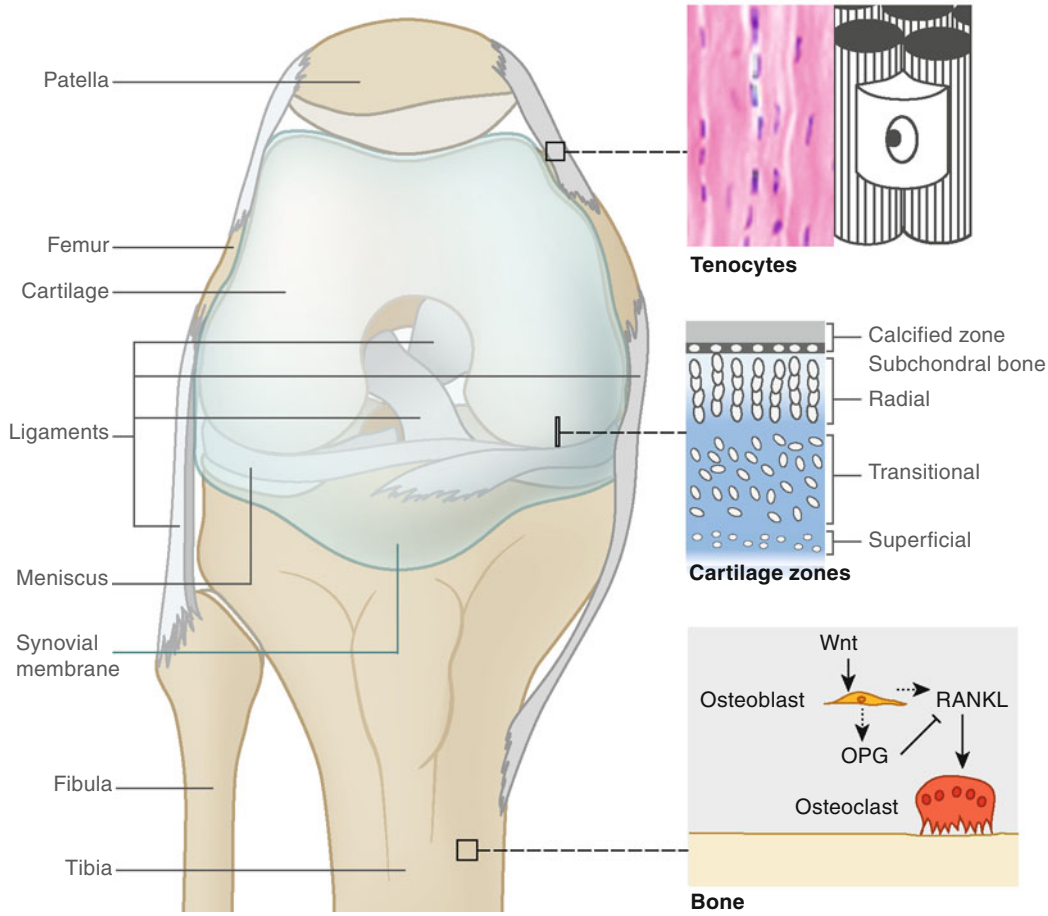

Fig. 1 Macroscopic and microscopic diagram of the anatomy of the human knee. The knee is a synovial joint; its anatomical structures, bones (patella, femur, fibula, and tibia), ligaments, and meniscus are shown (to the *left*), including the different cell compartments. The inserts to the *right* depict magnifications of important structures and tissue-specific pathways showing, from *top to bottom*, tendon, cartilage, and bone. Please note that the cartilage zones do not extend along the cartilage but into it, toward the femur, as indicated by the *small gray box*

Ligaments and Tendons

Tendons and ligaments are tough, fiber-rich connective tissues characterized by their excellent tensile strength. Both consist of fibroblasts (in tendons called tenocytes), which have long extensions that are located in rows in between the collagen fibrils, and the proteoglycan matrix that is synthesized by the fibroblasts into the intercellular space (Fig. 1). The collagen fibrils consist primarily of collagen type I and very small amounts of elastin and other collagens (types II–V, IX, and X).

Tendons are responsible for the power transmission as well as for the stabilization of joints and skeletal elements. In tendons the collagenous fibers, which are parallel and oriented in tensile direction, are divided by septa of loose connective tissue (peritendineum) to separate bundles. On the outside, the tendon is enveloped by a white fibrous sheath called epitendineum, which merges into the perimysium, the connective tissue surrounding the muscle.

Ligaments mediate the guidance of joints and skeletal elements. They are coarse, fiber-rich connective tissues that connect different skeletal

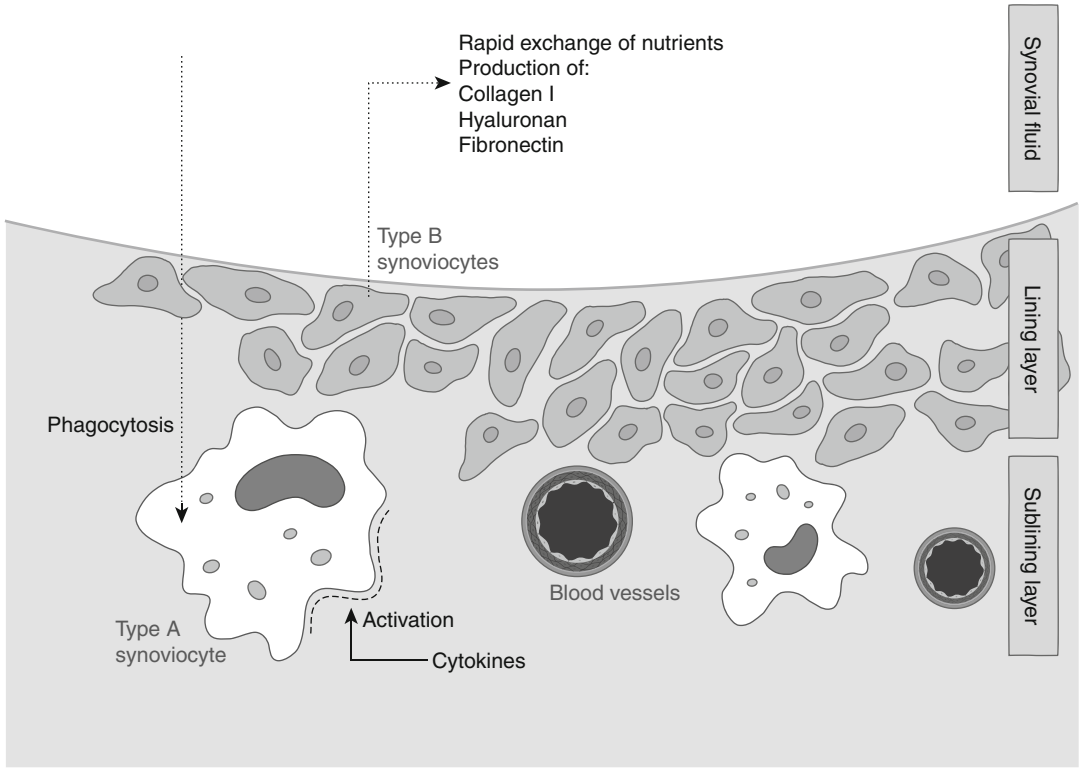

Fig. 2 Schematic view of the synovial membrane (or synovium) and its cell types. Type A synoviocytes are resident macrophages, which are rare in healthy synovium, and type B synoviocytes are fibroblast-like cells. Basal functions of these cell types are shown in black. The different layers of the synovium are labeled on the *right side*. As depicted, the sub-lining is extensively vascularized

elements and have mainly stabilizing functions. The histological structure of the ligament is very similar to the structure of tendons.

Damage of these structures due to a trauma commonly leads to an impairment of the joint function and may possibly result in changes of its biomechanical properties and subsequent osteoarthritis (see chapter "Osteoarthritis") [16]. Inflammatory processes, like in rheumatoid arthritis (see chapter "Rheumatoid arthritis"), can cause a chronic damage to the tendons, tendon sheaths, the articular capsule, and the ligaments, thus deforming the joints [17].

Synovium

The synovial membrane (or synovium, Fig. 2) is specific to synovial joints and seals the synovial fluid from the surrounding tissue. It is only about four to five cell layers thick and has no basement membrane, which makes it differ significantly from regular epithelium. The composition of the synovium is very variable, but mostly has two layers: the superficial layer of the synovium is called lining layer and can be separated histologically from the more loose network of fibroblast underneath, which is called sub-lining (Fig. 2). It consists of two cell types, fibroblasts and macrophages, which both differ from similar cells in other tissues. The (resident) macrophages are called type A synoviocytes and are rare in healthy synovium. Their main function is phagocytosis of undesirable substances from the synovial fluid, such as cell debris and dead cell tissues. The fibroblast-like type B synoviocytes provide the synovial cavity with lubricating factors and produce components of the extracellular matrix, including hyaluronan, collagens, and fibronectin. The superficial layer is called

lining layer. This layer of cells lacks the basement membrane and thereby facilitates the rapid exchange of nutrients between blood and the synovium.

The sub-lining is intensely vascularized, providing nutrients to the synovium and the avascular cartilage. During rheumatoid arthritis, type B synoviocytes undergo stable activation, meaning that they proliferate more and produce proinflammatory cytokines (see chapter "Rheumatoid arthritis").

Inside-In and Outside-In Signaling: Metabolites Affecting the Joints

Several morphogens and growth factors have been implicated in regulating the sensitive homeostasis of resting chondrocytes. Among others, three groups of soluble proteins regulate chondrocyte differentiation in endochondral ossification: bone morphogenetic proteins (BMPs), growth factors, and Wnts [18]. The stimulation of resting chondrocytes with these factors leads to a loss of the resting phenotype and induces hypertrophic differentiation or proliferation of chondrocytes.

As cartilage tissue is avascular and the chondrocytes are isolated inside their lacunae, the communication between chondrocytes in the superficial zone and chondrocytes in the middle and deeper layers occurs through diffusion. Chondrocytes located in the superficial zone of adult cartilage communicate via gap junction channels consisting of connexin 43 and 45 [19].

The synovium plays an important role in the repair process induced by proinflammatory cytokines that are released in response to intra-articular damage [20]. Exposure to proinflammatory cytokines activates type A synoviocytes, which then function as tissue macrophages. The type B synoviocytes are also proposed to play a critical role in the switch from acute inflammation to adaptive immunity, tissue repair, as well as chronic inflammation. During chronic inflammation they can get stably activated, meaning that they fail to switch off their inflammatory program, leading to inappropriate survival and proliferation of type B synoviocytes and retention of leukocytes within the inflamed tissue. Due to these inflammatory conditions, there is an increase in vascularization of the sub-lining, facilitating the accumulation of immune cells and perpetuating possible autoimmune processes. These processes together lead to hyperplasia of the synovial membrane, and the resulting tissue is called pannus tissue [21].

Final Remarks

The joint does not only make movement possible, but functions as a highly specialized organ. The different compartments work together with an extensive crosstalk. If one part of the joint is damaged or impaired in function, it affects the whole joint, as seen, for example, during osteoarthritis (see chapter "Osteoarthritis") or rheumatoid arthritis (see chapter "Rheumatoid arthritis").

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