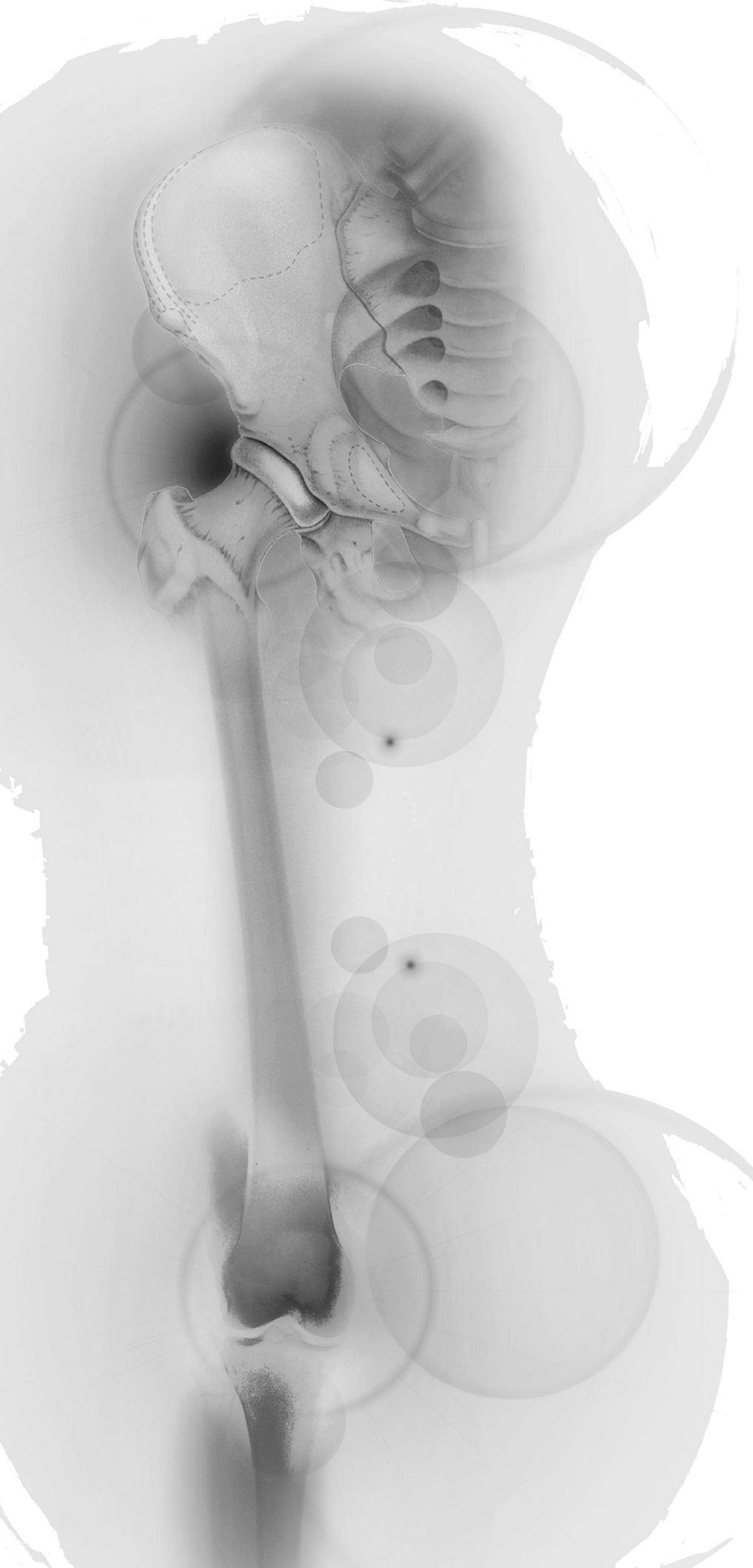

LIÇÕES

LIÇÕES

LIÇÃO 1

Moderadores: Jaime Branco e Lúcia Costa

RHEUMATOID ARTHRITIS: FROM INFLAMMATION TO EROSIONS

Georg Schett[1]
1. Department of Internal Medicine 3, Rheumatology and Immunology, University of Erlangen-Nuremberg, Germany

Arthritis is a perfect example for the clinical relevance of the interaction between inflammation and bone. Immune activation and inflammation in the course of arthritis affect profoundly influence bone remodeling. Typically, patients with rheumatoid arthritis suffer from bone erosions resulting from an excess of bone resorption. In rheumatoid arthritis proinflammatory cytokines such as TNF, IL-1 and IL-17 as well as PGE2 promote the synthesis of RANKL in the synovial membrane, which allows the local differentiation of osteoclasts and damage to the adjacent cortical bone surface. Anti-osteoclastogenic cytokines such as IFN , IL-4 and IL-10 do not compensate the effect of these proinflammatory mediators. Moreover, proinflammatory cytokines, in particular TNF, enhance the expression of Dkk-1 and sclerostin, which act as Wnt antagonists and effectively block bone resorption. Thus, inflammation in the context of rheumatoid arthritis enhances bone resorption while blocking bone formation and thus prevents adequate repair responses. In contrast to rheumatoid arthritis, other forms of joint inflammation such as spondylarthritides are associated with excessive bone formation at periosteal sites close to inflamed joints and the enthesial organs. Clinically these lesions appear as bony spurs. These bony spurs are based on enhanced bone formation, which is driven by the expression of bone morphogenic proteins as well as Wnt proteins. In summary, bone remodeling is crucial for the morphological differences of the various forms of arthritis. Insights into the molecular regulation of bone remodeling in arthritis allows to define specific therapeutic interventions to protect joints from inflammatory damage.

LIÇÃO 2

Moderadores: Helena Santos e Augusto Faustino

SPONDYLARTHRITIS: FROM INFLAMMATION TO OSTEOPROLIFERATION

Rik J. Lories[1]
1. Laboratory for Skeletal Development & Joint Disorders, Division of Rheumatology, Department of Musculoskeletal Sciences, KU Leuven, Belgium

The identification of specific proinflammatory cytokines (e.g. TNF) and immune cells in chronic arthritis has lead to the development of new targeted therapies. These drugs, in particular antibodies and soluble receptors directed against TNF, have an unprecedented effect on signs and symptoms of the disease. Activation of TNF and related cytokines also contributes to the process of joint destruction. Therefore in chronic joint diseases such as rheumatoid arthritis, inhibition of TNF does not only improve signs and symptoms but also positively affects the long-term outcome of the disease by preventing joint destruction. Ankylosing spondylitis is another chronic skeletal disorder that preferentially affects the spine and sacroiliac joints[1]. Its prevalence and burden are similar to that of rheumatoid arthritis[2]. The outcome of this disease is not determined by joint destruction but by progressive spine and joint ankylosis which together with ongoing inflammation lead to disability[3]. TNF blocking drugs are highly successful as symptomatic treatment in these patients but current clinical and experimental evidence does not support the concept that these drugs will also prevent further damage and hence long-term disability[4-6].

Progression of ankylosis has been linked to activation of developmental signaling pathways such as bone morphogenetic proteins (BMPs) and Wnts. Our group has demonstrated that inhibition of BMPs prevents and stabilizes ankylosis in a specific mouse model[7]. In contrast, inhibition of DKK1, a Wnt antagonist, shift the phenotype of destructive arthritis in human TNF transgenic mice towards remodeling with new bone formation and also triggers ankylosis of the sacroiliac joints[8,9].

Links and coupling between inflammation and activation of these pathways are a rapidly evolving research area which could lead to the identification of new therapeutic targets to prevent ankylosis. Emerging data indicate that biomechanical factors and microdamage could play an important role in this type of rheumatic disease and that these may provide an explanation for the unusual association of inflammation with new tissue formation. The preferred anatomic site for disease development is probably found in the enthesis, an anatomical zone in which tendons and ligaments insert into the underlying bone and therefore a site of mechanical strain[10]. We have put forward the entheseal stress hypothesis to explain the sequence of events in ankylosing spondylitis and to understand the differences between control of inflammation and disease progression[11]. In this hypothesis, we suggest that microdamage in the enthesis may act as trigger of disease with subsequent activation of two different processes: acute inflammation and progenitor cell activation. Under normal circumstances these activations would be short-lived and lead to restoration of tissue homeostasis. However, factors such as genetic susceptibility may sustain these processes leading to chronic disease in AS patients. New genetic data obtained in mouse models also appear to support this concept.

These clinical and experimental observations appear to be rapidly changing our understanding of AS and related disorders further separating this disease from rheumatoid arthritis and its associated concepts. The differences between these common forms of arthritis thereby trigger new questions and will hopefully lead to more specific targeted therapies adapted to the individual patient's needs.

References

Nota: Este texto já foi publicado com a referência: Lories RJ. Spondyloarthritis: from inflamation to osteoproliferation. Acta Reumatol Port 2010; 35: 422-423

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369:1379-1390.
2. Saraux A, Guedes C, Allain J, et al. Prevalence of rheumatoid arthritis and spondyloarthropathy in Brittany, France. J Rheumatol 1999;26:2622-2627.
3. Machado P, Landewe R, Braun J, Hermann KG, Baker D, van der HD. Both structural damage and inflammation of the spine contribute to impairment of spinal mobility in patients with ankylosing spondylitis. Ann Rheum Dis 2010;69:1465-1470.
4. van der Heijde D, Landewe R, Einstein S, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58:1324-1331.
5. van der Heijde D, Landewe R, Baraliakos X, et al. Radiographic findings following two years of infliximab therapy in patients with ankylosing spondylitis. Arthritis Rheum 2008;58:3063-3070.
6. van der HD, Salonen D, Weissman BN, et al. Assessment of radiographic progression in the spines of patients with ankylosing spondylitis treated with adalimumab for up to 2 years. Arthritis Res Ther 2009;11:R127.
7. Lories RJU, Derese I, Luyten FP. Modulation of Bone Morphogenetic Protein signaling inhibits the onset and progression of ankylosing enthesitis. J Clin Invest 2005;115:1571-1579.
8. Diarra D, Stolina M, Polzer K, et al. Dickkopf-1 is a master regulator of joint remodeling. Nat Med 2007;13:156-163.
9. Uderhardt S, Diarra D, Katzenbeisser J, et al. Blockade of Dickkopf-1 induces fusion of sacroiliac joints. Ann Rheum Dis 2009.
10. Benjamin M, McGonagle D. The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. J Anat 2001;199(Pt 5):503-526.
11. Lories RJ, Luyten FP, De Vlam K. Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. Arthritis Res Ther 2009;11:221.

LIÇÃO 3

Moderadores: Domingos Araújo e Armando Malcata

ÉTICA DA DECISÃO POLÍTICA EM SAÚDE E TERAPÊUTICAS INOVADORAS

Maria do Céu Machado