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Chapter 1 : Bone Loss Triggered by the Cytokine Network in Inflammatory Autoimmune Diseases

Summary: Inflammatory bowel disease (IBD) is a complex genetic disease known to be associated with over susceptibility genetic loci. However, the pathophysiologic impact of the majority of these genetic loci is unclear.

Atherosclerosis Atherosclerosis, formerly considered a bland lipid storage disease, actually involves an ongoing inflammatory response. Recent advances in basic science have established a fundamental role for inflammation in mediating all stages of this disease from initiation through progression and, ultimately, the thrombotic complications of atherosclerosis. These new findings provide important links between risk factors and the mechanisms of atherogenesis. Clinical studies have shown that this emerging biology of inflammation in atherosclerosis applies directly to human patients. Elevation in markers of inflammation predicts outcomes of patients with acute coronary syndromes, independently of myocardial damage. In addition, low-grade chronic inflammation, as indicated by levels of the inflammatory marker C-reactive protein , prospectively defines risk of atherosclerotic complications, thus adding to prognostic information provided by traditional risk factors. Moreover, certain treatments that reduce coronary risk also limit inflammation. In the case of lipid lowering with statins, this anti-inflammatory effect does not appear to correlate with reduction in low-density lipoprotein levels. These new insights into inflammation in atherosclerosis not only increase our understanding of this disease but also have practical clinical applications in risk stratification and targeting of therapy for this scourge of growing worldwide importance. A common example is hay fever , which is caused by a hypersensitive response by mast cells to allergens. Pre-sensitised mast cells respond by degranulating , releasing vasoactive chemicals such as histamine. These chemicals propagate an excessive inflammatory response characterised by blood vessel dilation, production of pro-inflammatory molecules, cytokine release, and recruitment of leukocytes. Myopathies[edit] Inflammatory myopathies are caused by the immune system inappropriately attacking components of muscle, leading to signs of muscle inflammation. They may occur in conjunction with other immune disorders, such as systemic sclerosis , and include dermatomyositis , polymyositis , and inclusion body myositis. In addition, diseases affecting the bone marrow may result in abnormal or few leukocytes. Pharmacological[edit] Certain drugs or exogenous chemical compounds are known to affect inflammation. Vitamin A deficiency causes an increase in inflammatory responses, [20] and anti-inflammatory drugs work specifically by inhibiting the enzymes that produce inflammatory eicosanoids. Certain illicit drugs such as cocaine and ecstasy may exert some of their detrimental effects by activating transcription factors intimately involved with inflammation e. Such an approach may limit side effects that are unrelated to the tumor of interest, and may help preserve vital homeostatic functions and developmental processes in the organism. According to a review of , recent data suggests that cancer-related inflammation CRI may lead to accumulation of random genetic alterations in cancer cells. DNA damages may cause genetic mutations due to inaccurate repair. In addition, mistakes in the DNA repair process may cause epigenetic alterations. Typically, several hundreds to thousands of genes are methylated in a cancer cell see DNA methylation in cancer. DNA repair genes, in particular, are frequently inactivated by methylation in various cancers see hypermethylation of DNA repair genes in cancer. A report [41] evaluated the relative importance of mutations and epigenetic alterations in progression to two different types of cancer. This report showed that epigenetic alterations were much more important than mutations in generating gastric cancers associated with inflammation. HIV and AIDS[edit] It has long been recognized that infection with HIV is characterized not only by development of profound immunodeficiency but also by sustained inflammation and immune activation. Animal studies also support the relationship between immune activation and progressive cellular immune deficiency: SIV sm infection of its natural nonhuman primate hosts, the sooty mangabey , causes high-level viral replication but limited evidence of disease. Recent studies demonstrated that caspase-1 -mediated pyroptosis , a highly inflammatory form of programmed cell death, drives CD4 T-cell depletion and inflammation by HIV. Pyroptosis appears to create a pathogenic vicious cycle in which dying CD4 T cells and

other immune cells including macrophages and neutrophils release inflammatory signals that recruit more cells into the infected lymphoid tissues to die. The feed-forward nature of this inflammatory response produces chronic inflammation and tissue injury. Such agents would almost certainly be used in combination with ART. Resolution of inflammation[edit] The inflammatory response must be actively terminated when no longer needed to prevent unnecessary "bystander" damage to tissues. Resolution of inflammation occurs by different mechanisms in different tissues. Mechanisms that serve to terminate inflammation include:

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Chapter 2 : Inflammatory bowel disease - Wikipedia

Chapter Inflammatory Bowel Disease Microcirculation and Diversion, Diverticular and Other Non-infectious Colitides.

Unintended weight loss When to see a doctor See your doctor if you experience a persistent change in your bowel habits or if you have any of the signs and symptoms of inflammatory bowel disease. Request an Appointment at Mayo Clinic Causes The exact cause of inflammatory bowel disease remains unknown. One possible cause is an immune system malfunction. When your immune system tries to fight off an invading virus or bacterium, an abnormal immune response causes the immune system to attack the cells in the digestive tract, too. Heredity also seems to play a role in that IBD is more common in people who have family members with the disease. Although whites have the highest risk of the disease, it can occur in any race. Although smoking may provide some protection against ulcerative colitis, the overall health benefits of not smoking make it important to try to quit. Therefore, it may be that environmental factors, including a diet high in fat or refined foods, play a role. People living in northern climates also seem to be at greater risk. Complications found in both conditions may include: Having IBD increases your risk of colon cancer. General colon cancer screening guidelines for people without IBD call for a colonoscopy every 10 years beginning at age Ask your doctor whether you need to have this test done sooner and more frequently. Skin, eye and joint inflammation. Certain disorders, including arthritis, skin lesions and eye inflammation uveitis , may occur during IBD flare-ups. Certain medications for IBD are associated with a small risk of developing certain cancers. Corticosteroids can be associated with a risk of osteoporosis, high blood pressure and other conditions. In this condition, inflammation causes scars within the bile ducts, eventually making them narrow and gradually causing liver damage. IBD increases the risk of blood clots in veins and arteries. Over time, parts of the bowel can thicken and narrow, which may block the flow of digestive contents. You may require surgery to remove the diseased portion of your bowel. Diarrhea, abdominal pain and cramping may make it difficult for you to eat or for your intestine to absorb enough nutrients to keep you nourished. Chronic inflammation can lead to open sores ulcers anywhere in your digestive tract, including your mouth and anus, and in the genital area perineum. Sometimes ulcers can extend completely through the intestinal wall, creating a fistula â€” an abnormal connection between different body parts. Fistulas near or around the anal area perianal are the most common kind. In some cases, a fistula may become infected and form an abscess. This is a small tear in the tissue that lines the anus or in the skin around the anus where infections can occur. Complications of ulcerative colitis may include: Ulcerative colitis may cause the colon to rapidly widen and swell, a serious condition known as toxic megacolon. A hole in the colon perforated colon. A perforated colon most commonly is caused by toxic megacolon, but it may also occur on its own. Excessive diarrhea can result in dehydration.

Chapter 3 : Crohn's Disease vs Ulcerative Colitis : IBD | MEDCHROME

IBD Blog Follow the discussion on the latest advances in treating Crohn's disease and ulcerative colitis. Inflammatory bowel disease (IBD) is an umbrella term used to describe disorders that involve chronic inflammation of your digestive tract.

This is an open access article distributed under the Creative Commons Attribution License , which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. Abstract Bone remodeling is a lifelong process in vertebrates that relies on the correct balance between bone resorption by osteoclasts and bone formation by osteoblasts. Bone loss and fracture risk are implicated in inflammatory autoimmune diseases such as rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and systemic lupus erythematosus. The network of inflammatory cytokines produced during chronic inflammation induces an uncoupling of bone formation and resorption, resulting in significant bone loss in patients with inflammatory autoimmune diseases. Here, we review and discuss the involvement of the inflammatory cytokine network in the pathophysiological aspects and the therapeutic advances in inflammatory autoimmune diseases. Introduction Bone is the main calcified tissue of vertebrates and serves multiple functions including mechanical support, protection, and storage [1]. Bone is continuously maintained by the process of bone remodeling through clusters of bone-resorbing osteoclasts and bone-forming osteoblasts [1 , 3]. During bone remodeling, old or damaged bone is removed by osteoclasts and replaced by new bone formed by osteoblasts over several weeks [1 , 3]. Osteoblasts are of mesenchymal origin and function primarily as bone-forming cells [1 , 4]. Osteoblasts secrete the organic matrix, which predominantly contains collagen, and induce calcification during the process of new bone formation [5]. During bone remodeling, osteoblasts rebuild the bone matrix in regions where the bone has been resorbed by osteoclasts [1 , 4]. The differentiation and function of osteoblasts are regulated by the activation of transcription factors i. At the end of the bone-forming phase during bone remodeling, osteoblasts incorporate into the bone as osteocytes and the rest either remain on the bone surface as lining cells or undergo apoptosis [5 , 16]. Osteocytes are former osteoblasts that become trapped during the process of bone deposition and remain regularly distributed throughout the mineralized bone matrix. Osteocytes are the primary mechanosensory cells that act as regulators of mineral metabolism during bone remodeling [17]. Studies have revealed that osteocytes can send signals of bone resorption to osteoclasts during bone remodeling [17 , 18]. The process of bone remodeling depends on the tight coupling of bone formation and bone resorption to ensure that there is no net change in the bone mass and to maintain the quality after each remodeling cycle [1 , 3 , 4]. An imbalance in this process is closely linked to various types of bone diseases, such as osteoporosis, osteopetrosis, periodontitis, and rheumatoid arthritis RA [19]. Osteoporosis is a skeletal disorder characterized by compromised bone strength, predisposing patients to an increased risk of fracture [20]. Osteoporosis was first considered to be an age-related disorder characterized by low bone mass and increased bone fragility, thereby putting the patient at risk of fractures. However, over time, it has come to be viewed as a heterogeneous condition that can occur at any age and its etiology is attributed to various endocrine, metabolic, and mechanical factors [19]. Studies have reported an increased risk of developing osteoporosis in patients with various inflammatory conditions [1 â€” 4]. Inflammation is characterized by the activation of several cell populations of the innate and adaptive immune system that produce inflammatory cytokines [21]. Inflammation perturbs normal bone homeostasis and is known to induce bone loss because it promotes both local cartilage degradation and local and systemic bone destruction by osteoclasts and inhibits bone formation by osteoblasts Figure 1. The role of inflammatory cytokine network in inflammatory bone loss. Bone remodeling is tightly regulated by the balanced action between bone-forming osteoblasts and bone-resorbing osteoclasts. In chronic inflammatory condition, inflammatory cytokine networks induce an uncoupling of bone formation and resorption that result in significant inflammatory bone loss. Inflammatory joint diseases share in

common the presence of an inflammatory process that targets the joints, with adverse effects on structure and function [22]. RA is one of the most common autoimmune diseases that results in chronic inflammation of the joints [23]. Autoimmune diseases are characterized by impaired function and destruction of tissues caused by the presence of autoantibodies due to abnormally activated lymphocytes and nonlymphoid cells, such as macrophages, dendritic cells, and fibroblasts [24 , 25]. Dysregulation of inflammatory or anti-inflammatory cytokine production or action is reported to play a central role in the pathogenesis of autoimmune diseases such as RA, ankylosing spondylitis AS , inflammatory bowel disease IBD , and systemic lupus erythematosus SLE [26 â€” 32]. These studies have demonstrated a possible link between chronic inflammation and the pathogenesis of autoimmune diseases. Moreover, chronic inflammatory autoimmune diseases are frequently associated with bone destruction [38]. Bone loss is commonly observed in inflammatory joint diseases such as RA and AS [22]. Although a large number of studies have focused on inflammatory autoimmune diseases over the past 10 years, the role of the inflammatory cytokine network involved in bone loss in patients with inflammatory autoimmune diseases has not been well addressed. Therefore, in this review, we will provide an overview of the interaction between inflammatory autoimmune diseases and bone destruction through the regulation of the inflammatory cytokine network. We specifically focused on how bone loss and fracture risk are implicated in inflammatory autoimmune diseases. Rheumatoid Arthritis RA RA is a chronic autoimmune inflammatory disease characterized by the production of two main autoantibodies, rheumatoid factor and anticitrullinated peptide antibody, against common autoantigens that are widely expressed outside the joints, thereby resulting in local bone erosion, joint space narrowing, and extra-articular manifestations [23 , 39]. In severe cases, RA can lead to periarticular osteopenia, systemic osteoporosis, and systemic bone erosion [40]. Disturbance of bone homeostasis in RA patients is driven by the cellular action of osteoclasts [41]. The enhanced osteoclast formation and activation is due to the increased accumulation of osteoclastogenic factors in the inflamed synovium [42 â€” 45]. In RA, elevated inflammatory cytokines have been implicated in bone destruction through recruitment of osteoclast precursors to the bone environment, where they differentiate into mature osteoclasts [46 â€” 48]. These anti-inflammatory cytokines have a negative effect on the joint destruction and inflammation associated with RA [55]. The blockade of Dkk-1 inhibits local bone resorption by reducing osteoclast numbers through the downregulation of OPG expression in the joints; this is further compounded because OPG regulates Dkk-1 expression through a feedback loop [60]. A study by Smolen et al. IL-1 is a key regulatory cytokine in mouse models of inflammatory arthritis. In TNF-transgenic mice lacking IL-1 signaling, cartilage destruction is completely blocked and bone destruction partly reduced despite the presence of synovial inflammation, indicating that TNF-induced local bone destruction and systemic inflammatory bone loss are largely dependent on IL-1 [48]. Studies have shown that the IL-6 antagonist tocilizumab has a beneficial effect on joint destruction and disease progression in RA patients [72 , 73]. IL is the most recently described subclass of inflammatory cytokines. IL induces the secretion of proinflammatory cytokines i. These elevated inflammatory cytokines and chemokines serve to activate and recruit neutrophils, macrophages, and lymphocytes to the inflamed synovium, thereby enhancing synovial inflammation [82]. Intra-articular injection of recombinant IL also results in joint inflammation and damage [79 , 83]. The role of IL as a potent stimulator of osteoclastogenesis in RA patients was first demonstrated by Kotake et al. In animal model studies, therapeutic approaches using IL antibodies or a soluble IL receptor have resulted in significant suppression of joint inflammation and bone erosion through downregulation of synovial RANKL and inflammatory cytokine expression [92 â€” 94]. In conclusion, bone destruction in RA is caused by a complex network of inflammatory cytokines, resulting in the chronic inflammation of the synovium. These studies have revealed several promising targets for the treatment of inflammatory bone loss in RA. Ankylosing Spondylitis AS AS is a systemic rheumatic disease characterized by chronic inflammation that chiefly affects the sacroiliac joints and the spine, whereas RA primarily affects the synovial membrane [95 , 96]. One of the main features of structural damage in AS is bony ankyloses characterized by excessive bone formation that

leads to the formation of bone spurs, such as syndesmophytes and enthesophytes, that contribute to ankylosis of the joints and poor physical function [96]. Moreover, the excessive loss of trabecular bone in the center of the vertebral body causing osteopenia or osteoporosis and leading to vertebral fractures with increased spinal deformity has been documented in AS patients [97]. However, little or no effect on structural remodeling is achieved [99]. However, antibody therapies blocking IL-6R signaling with tocilizumab or sarilumab failed to show clinical efficacy in a phase II clinical trial with AS patients, suggesting that IL-6 is not a pivotal inflammatory cytokine in the pathogenesis of AS [,]. The involvement of Th17 cells in the promotion of the inflammatory process in AS patients is shown by the significantly elevated levels of Th17 cells in the peripheral blood of patients with AS [,]. Moreover, antibody therapies such as blocking IL with secukinumab were shown to significantly downregulate the signs, symptoms, and objective parameters of inflammation in a phase II clinical trial in AS patients [ ]. Currently, phase III clinical trials consisting of antibody therapy with secukinumab in AS patients are ongoing [ ]. Ulcerative colitis is limited to the colon area; common symptoms include rectal bleeding, frequent stools, mucus discharge from the rectum, tenesmus, and lower abdominal pain [ ]. Therefore, Th1, Th2, and Th17 cells seem to be broadly involved in the pathogenesis of IBD through the regulation of inflammatory cytokine network. Interestingly, low bone matrix density BMD defined as osteopenia or osteoporosis is a known chronic complication of IBD [ ]. Although IBD is not the sole risk factor for developing osteoporotic bone loss, it appears to be related to other known osteoporosis risk factors such as age, sex, body mass index, and medication [ ]. Thus, the acceleration of the development of new biological drugs for IBD requires expanded insights into understanding the physiology, mechanism, and pathogenesis of IBD. The principal mechanisms behind reduced BMD in IBD patients are still not completely understood, but a complex network of inflammatory cytokines that influence bone destruction has been reported [,]. Mucosal and systemic concentrations of many pro- and anti-inflammatory cytokines are elevated in IBD patients [ ]. These proinflammatory cytokines stimulate bone resorption by osteoclasts through the induction of RANKL expression [1 , 4]. IL secreted by Th17 cells is one of the crucial cytokines involved in the pathogenesis of IBD via the induction of Th1 and Th17 immune responses in the gut [ ]. IL, a new member of the IL-1 family, is a ligand for the IL-1 receptor-related protein ST2 that is anticipated to be essential for the induction of Th2 immune responses [ ]. Enhanced IL levels are closely associated with IBD, particularly in ulcerative colitis patients [ ]. Correspondingly, the inhibition of IL signaling through anti-ST2 antibody treatment attenuates the severity of arthritis in an animal RA model [ ]. Furthermore, IL stimulates human osteoclast differentiation through the activation of ST2 receptor signaling [ ]. However, approximately one-third of the patients benefit minimally or not at all from this treatment [,]. Therefore, new drugs targeting other inflammatory cytokines could potentially be useful for treating IBD patients who do not respond to anti-TNF therapy [ ]. Systemic Lupus Erythematosus SLE SLE is an autoimmune disease that predominantly affects young women and is characterized by immunological hyperactivity and multiorgan damage. The exact causative factors of SLE are still unknown [ ]. Unrestricted hyperactivation of the immune system may lead to the overproduction of autoantibodies, immune complex deposition, and inflammatory cytokine release, eventually resulting in the SLE phenotype [ ]. Autoantibodies bound with antigens are deposited in organs, thereby causing chronic inflammation and tissue damage [ ]. Abnormal IL-6 levels were also observed in both serum and local tissues in patients with SLE [ ]. The dominant role of IL-6 in SLE pathogenesis is to accelerate autoantibody production by promoting the proliferation of autoreactive B cells [ ]. Interestingly, it has been reported that IL-6 produced by dendritic cells inhibits Treg cell function in mouse SLE models [ ]. Thus, IL-6 is implicated as the most important inflammatory cytokine in the pathogenesis of SLE, and antibody therapies blocking IL-6 receptor signaling with tocilizumab are reported to be effective in treating SLE [ ]. IL is a proinflammatory cytokine with multiple functions in the regulation of tissue inflammation [ ]. The IFN signature produced by pDCs can promote the pathogenesis of SLE by enhancing autoantibody production and activating Th17 cells to secrete cytokines [â€”]. There seems to be a high prevalence of osteoporosis in SLE patients, but the prevalence frequencies differ widely as a consequence of differences in

body mass, age, sex, ethnicity, disease severity, and medication use [ ]. Glucocorticoid use, longer disease duration due to chronic inflammation, neuropsychiatric disease complications, and previous fractures were identified as associated factors for SLE-related osteoporotic fractures [ ]. Although the direct correlation between inflammatory cytokine levels and bone defects in SLE patients remains unclear, bone destruction in SLE patients is thought to be the result of accelerated osteoclastogenesis induced by proinflammatory cytokines [ ]. Furthermore, a recent study by Tang et al. Discussion Bone remodeling is a highly coordinated process that involves bone resorption and formation, which are essential for repairing damaged bones and maintaining mineral homeostasis. However, in chronic inflammatory conditions, the inflammatory cytokine network induces an uncoupling of bone formation and resorption that results in significant inflammatory bone loss. However, the effects of inflammatory cytokines on inflammatory bone loss and in the pathogenesis of inflammatory autoimmune diseases are more complicated. As discussed in this review, bone loss in inflammatory autoimmune diseases may be caused by direct or indirect effects with complicated mechanisms by inflammatory cytokines or the inflammatory cytokine network in chronically inflamed tissues. Therefore, drugs targeting multiple cytokines could be an effective strategy for disease prevention and reducing disease progression. Inflammatory autoimmune diseases continue to be a mounting public health concern worldwide.

Chapter 4 : Inflammation - Wikipedia

It is one of the two major forms of inflammatory bowel disease, the other being ulcerative colitis. Genetics, microbes, food, and other environmental factors can cause or propagate this condition.

Chapter 5 : Scientific programme

The idiopathic inflammatory bowel diseases comprise two types of chronic intestinal disorders: Crohn's disease and ulcerative colitis. Accumulating evidence suggests that inflammatory bowel disease results from an inappropriate inflammatory response to intestinal microbes in a genetically susceptible host.

Chapter 6 : Inflammatory bowel disease (IBD) - Symptoms and causes - Mayo Clinic

NOD2 and Crohn's Disease. The importance of responses to intestinal bacteria in inflammatory bowel disease is highlighted by the association between Crohn's disease and the NOD2 gene 77 (), which.

Chapter 7 : Inflammatory Bowel Disease | Clinical Gate

INTRODUCTION. Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the intestine that causes abdominal pain, diarrhea, and weight loss and includes two forms, Crohn's disease and ulcerative colitis[].

Chapter 8 : Inflammatory Bowel Disease Center - Massachusetts General Hospital, Boston, MA

(pages) Gil Y. Melmed nucleotide concentrations and thiopurine-induced leukopenia in the treatment of inflammatory bowel disease Basic Science.

Chapter 9 : Volume 6 Issue 1 | Inflammatory Bowel Diseases | Oxford Academic

A recent study in a preclinical model of inflammatory bowel disease shows dietary exposure to bisphenol-A, or BPA, found in polycarbonate plastics and epoxy resins, can increase mortality and.