Osteoarthritis and Cartilage 21 (2013) 1813–1823

Osteoarthritis and Cartilage

Review

Osteoimmunology in mucopolysaccharidoses type I, II, VI and VII. Immunological regulation of the osteoarticular system in the course of metabolic inflammation

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ARTICLE INFO

Article history:
Received 22 October 2012
Accepted 3 August 2013

Keywords:
Mucopolysaccharidosis
Metabolic inflammation
Osteoimmunology
Dysostosis multiplex
anti-TNF

SUMMARY

Background: Mucopolysaccharidoses (MPSs) are rare genetic diseases caused by a deficient activity of one of the lysosomal enzymes involved in the glycosaminoglycan (GAG) breakdown pathway. These metabolic blocks lead to the accumulation of GAGs in various organs and tissues, resulting in a multi-systemic clinical picture. The pathological GAG accumulation begins a cascade of interrelated responses: metabolic, inflammatory and immunological with systemic effects. Metabolic inflammation, secondary to GAG storage, is a significant cause of osteoarticular symptoms in MPS disorders.

Objective and method: The aim of this review is to present recent progress in the understanding of the role of inflammatory and immune processes in the pathophysiology of osteoarticular symptoms in MPS disorders and potential therapeutic interventions based on published reports in MPS patients and studies in animal models.

Results and conclusions: The immune and skeletal systems have a number of shared regulatory molecules and many relationships between bone disorders and aberrant immune responses in MPS can be explained by osteoimmunology. The treatment options currently available are not sufficiently effective in the prevention, inhibition and treatment of osteoarticular symptoms in MPS disease. A lot can be learnt from interactions between skeletal and immune systems in autoimmune diseases such as rheumatoid arthritis (RA) and similarities between RA and MPS point to the possibility of using the experience with RA in the treatment of MPS in the future. The use of different anti-inflammatory drugs requires further study, but it seems to be an important direction for new therapeutic options for MPS patients.

Introduction

Mucopolysaccharidoses (MPSs) are a group of 11 inherited, genetically conditioned, metabolic, more pronounced in connective tissue disorders, with systemic and progressive course.

The most typical description includes characteristic facial features, cardiac, pulmonary, neurological, ophthalmic and auditory symptoms, hepatosplenomegaly, abdominal and/or inguinal hernia, early accelerated growth and later growth retardation[1–6]. The occurrence of musculoskeletal symptoms is characteristic for all types of the disease, except for MPS III.

Skeletal abnormalities are associated with storage of glycosaminoglycans (GAGs) such as dermatan sulfate (DS), chondroitin sulfate (CS) or keratan sulfate (KS), while storage of heparan sulfate (HS) is associated central nervous system pathology[7].

Joint stiffness and contractures might be found, except for MPS IV in which there is joint laxity. Other major osteoarticular manifestations of MPS are claw hands, thoracolumbar kyphosis, scoliosis, odontoid hypoplasia, hip dysplasia, genu valgum and pectus carinatum. Characteristic bone changes in imaging studies are defined as dysostosis multiplex (Fig. 1)[8].

Clinical symptoms observed in patients with MPS are a consequence of a deficient activity of lysosomal enzymes that leads to

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http://dx.doi.org/10.1016/j.joca.2013.08.001

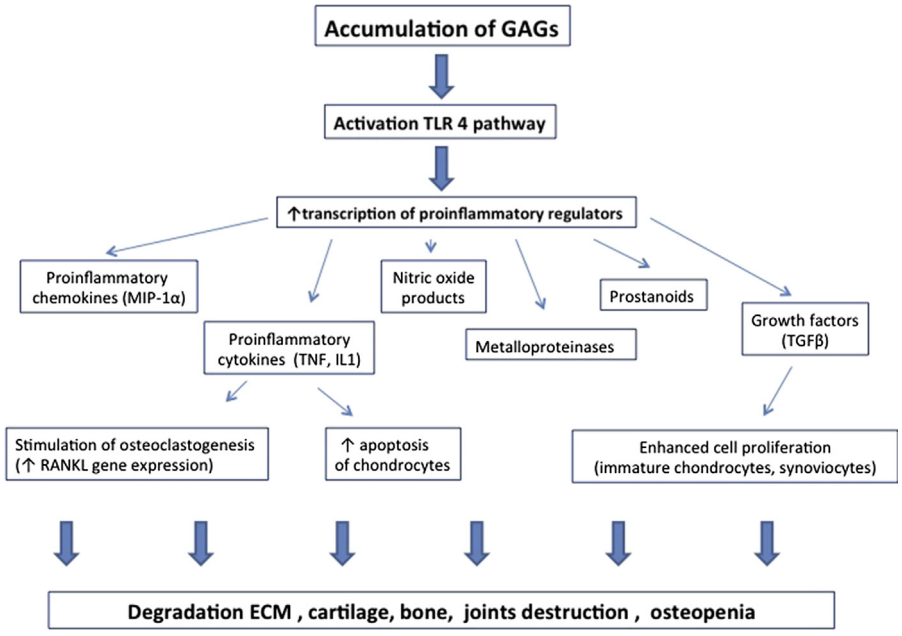

Fig. 1. Metabolic inflammation in MPS disease. IL-1 – interleukin 1β

intra-lysosomal and extra-lysosomal GAGs storage. The accumulation of GAGs is the beginning of a cascade of interrelated responses: metabolic, inflammatory, and immunological with systemic effects[9].

The immune and skeletal systems have a number of shared regulatory molecules, including cytokines, receptors, signaling molecules, and transcription factors. Recognition of the complex interactions between the immune system and bone led to the development of the interdisciplinary research field osteoimmunology, which aims to understand the molecular mechanisms between the skeletal and immune systems[10–13].

The aim of this review is to present recent progress in the understanding of the role of inflammatory and immune processes in the pathophysiology of osteoarticular symptoms in MPS disorders. In order to develop new effective therapeutic strategies for MPS disease, attention should be paid to the relationship between bone disorders and aberrant immune responses.

Metabolic inflammation in MPS diseases (Fig. 1)

GAGs interact with a wide range of proteins involved in physiological and pathological processes, including chemokines, cytokines, growth factors, morphogens, enzymes, and adhesion molecules[14].

GAGs might induce inflammation in different cells. Simonaro *et al.* demonstrated that in normal chondrocytes of healthy rats, DS might stimulate nitric oxide (NO) release from and elicit apoptosis effects on chondrocytes[15]. Wang *et al.* showed that administration of GAGs such as hyaluronic acid, HS and CS A, B, and C to normal mice induces signs of inflammation: arthritis, tendosynovitis, dermatitis, and cellular infiltrates in various connective tissues[16]. Circulating or locally released GAGs induced the clonal expansion of various cells include lymphocytes T, lymphocytes B, and macrophages. These findings indicate that immunization against self-antigens like GAGs alters the immune system and causes systemic chronic inflammation disorder[16].

Immune response and metabolic regulation are highly integrated and the proper function of each is dependent on the other[17–19]. Hotamisligil proposed a term “metaflammation” (metabolically triggered inflammation) for a condition principally triggered by nutrients and, engaging a similar set of molecules and signaling pathways to those involved in classical inflammation[17]. The long-term consequences of prolonged inflammation are often not beneficial and in many disorders normal immune response is turned into a permitting process leading to damage. In metabolic inflammation in MPS, the factor that induces an immune process is a metabolic surplus of GAGs.

DiRosario *et al.* study of MPS IIIB mouse brain demonstrated significant up-regulation of numerous immune-related genes of innate and adaptive immune cells and molecules, including T cells, B cells, complement, immunoglobulin, Toll-like receptors (TLR), and molecules essential for antigen presentation[20]. Killedar *et al.* showed that lymphocytes from MPS IIIB mice transferred to naïve mice cause neuroinflammation with increased expression of proinflammatory cytokines and lymphocyte infiltration[21].

Tessitore *et al.* as well as Simonaro *et al.* demonstrated that the loss of degradation and recycling of GAGs results in an imbalance of cellular homeostasis, reduces functionality of lysosomes with impairs autophagy, accumulation of polyubiquitinated proteins and mitochondrial function in MPS VI human fibroblasts leading to overproduction of reactive oxygen species[22,23].

Osteoimmunological aspects of osteoarticular disorder in MPS

Synovial inflammation

The synovial membrane in animals and patients with MPS VI and VII shows characteristics of hyperplasia. Studies demonstrated that MPS VI and VII animals' synovial cells proliferate at a faster rate than normal cells[15,23,24]. No apoptosis was observed in these cells (in contrast to MPS chondrocytes). Hyperproliferation could result indirectly from increased levels of tumor necrosis factor (TNF)-alpha and interleukin (IL)-1 and elevated levels of the prosurvival lipid S1P. Levels of these cytokines are also markedly elevated in synovial fluid animals with MPS VI and VII[25].

Articular and growth cartilages disorder

Growth and bone remodeling in MPS

Articular and growth cartilage is the main place of pathology in the osteoarticular system in MPS[25]. Studies in MPS VI and VII