NEW HORIZONS

AlphaV Beta 3 Integrin: A Novel Therapeutic Target in Rheumatoid Arthritis

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Introduction:

Integrins AlphaV beta3 (Vitronectin receptor) belongs to the major family of cell surface receptors. Structurally it is a heterodimeric transmembrane proteins formed by non-covalent association of 125 kDa alpha V and 105 kDa beta 3 subunits. Both subunits are type1 membrane proteins with large extracellular ectodomains and short cytoplasmic tails (1,2). Vitronectin receptor has distinct functional properties that are mediated through interactions with a variety of extracellular matrix (ECM) proteins in addition to vitronectin. These ECM proteins include osteopontin, bone sialoprotein, fibronectin, fibrinogen, thrombospondin, proteolysed collagen, Von Willebrand factor, and others. These interactions play a part in regulating intracellular signalling, cell migration, cell proliferation, and cell survival (1-3).

AlphaV beta3 integrin is expressed at low levels in most normal tissues including intestinal, vascular, and smooth muscle cells, but, of particular interest, is that high level expression is limited to bone, the mid-menstrual cycle endometrium, placenta, inflammatory sites, and invasive tumours. The cell types that express high levels of this integrin include mature, bone resorbing osteoclasts and activated macrophages, a small fraction of neutrophils, angiogenic endothelial cells, and migrating smooth muscle cells (2,3).

Integrin alpha V beta 3 (vitronectin receptor) has been the focus of intensive research because of its major role in several distinct processes, particularly osteoclast mediated bone resorption (3-5), angiogenesis (pathological neovascularisation) (6,7) and macrophage dependent inflammation (8,9) as depicted in (Fig. 1), which carry important relation with rheumatoid arthritis. Patho-physiological role in rheumatoid arthritis

a) Macrophage dependent inflammation

The integrin alpha V beta 3 is highly expressed on activated macrophages and osteoclasts (8). These cell types are found in abundance at sites of bone destruction in RA patients - that is, activated macrophages are markedly increased in both subchondral bone and inflamed synovial tissue, and osteoclasts are markedly increased in subchondral bone at sites of bone erosion and resorption. Moreover, during inflammatory diseases such as RA, tumour necrosis factor (TNFα) and interleukin 1 (IL1) also significantly amplify osteoclastogenesis and generation of activated macrophages (9).

b) Osteoclast mediated bone resorption (5,6)

Activated alphaV and beta3 integrin promotes osteoclast migration to its ligand osteopontin an enhances osteoclast mediated bone resorption.

c) Inflammatory angiogenesis (6,7)

In addition, endothelial cells in rheumatoid synovium are subject to continuous production of angiogenic stimuli (TNFα) & vascular endothelial growth factor (VEGF), resulting in the expression of alphaV beta3 on sprouting
endothelial cell buds and new blood vessel development (pathological neovascularisation) (10). Recently, osteopontin (OPN), one of extracellular matrix protein which is a known agonist of alphaV beta3 receptor is suggested to have the possible role in the vascularisation of inflamed synovial tissue in humans with chronic idiopathic arthritis. Hence, indicating possible correlation of alphaV beta3 receptor in the pathological angiogenesis in chronic idiopathic arthritis patients (12).

As osteoclast mediated bone resorption and macrophage dependent inflammation and inflammatory angiogenesis are such a central pathogenic feature of RA (10,11). Therefore, these facts support the view that inhibition of alpha V beta 3 in the synovium of RA patients may have therapeutic benefits.

The therapeutic-potentials in rheumatoid arthritis (RA)

Intraarticular administration of a cyclic peptide alpha V beta 3 antagonist to rabbits with antigen induced arthritis, a model with features that resemble RA, inhibits synovial angiogenesis, inflammatory cell infiltration, and bone and cartilage destruction (13). In addition, SB 273005, a non-peptide antagonist of alpha V beta 3, is reported to significantly reduce swelling and the destruction of both bone and cartilage in adjuvant-induced model of arthritis in the LEW rat (14). More recently, the role of osteopontin has been examined in an experimental RA model. Osteopontin deficiency prevent the mice from such surface destruction, loss of proteoglycan in the articular joint cartilage, and swelling of the joints (15). Thereby indicating potential role of alpha V beta 3 antagonism in RA. Vmathixin, also known as M EDI-522, is a humanised monoclonal IgG1 antibody that specifically binds a conformational epitope formed by both the integrin alphaV and beta3 subunits. It blocks the interaction of alphaV beta3 with various ligands such as osteopontin and vitronectin. It is in phase II trials for the potential treatment of leiomyosarcoma and is also being studied in phase I trials as an anti-inflammatory and potential rheumatoid arthritis therapy (16). Recently, a new most potent and selective alphaV beta3 antagonist, in rat adjuvant-induced arthritis. Arthritis Rheum 2001; 44: 128–37.

Conclusion

The antagonists of integrin alphaV beta3, receptor, have been the focus of intensive research to develop them as novel drugs for RA because of its major role in osteoclast mediated bone resorption, macrophage dependent inflammation and inflammatory angiogenesis which are considered as central pathogenic feature of rheumatoid arthritis.

References