Angiotensin converting enzyme in rheumatoid arthritis

Sirs: Being interested in vascular endothelial cell transdifferentiation, I read with interest the instructive articles by Veale et al and Goto et al about the angiotensin converting enzyme production in rheumatoid arthritis. Although there is no doubt that vascular endothelial cells participate in this process, the role of macrophages remains questionable because the antibodies used for their identification (antigen CD14) are not macrophage specific and cross react with vascular endothelial cells. Moreover, undifferentiated vascular endothelial cells can transdifferentiate into macrophage-like cells and migrate into the extravascular space. It may be useful to re-evaluate the role of macrophages in rheumatoid arthritis in the light of the new knowledge about the transdifferentiation of vascular endothelium. For example, the mesenchymal transformation cell responsible for joint destruction differentiates into fibroblasts in due course and are not, therefore, inflammatory cells. McCachen considers, however, any collagenase producing cells immuno-competent with Leu-M3 or HAM56 to be macrophages. Again, these antibodies are not macrophage specific and cross react with vascular endothelial cells. It is mesenchymal transformation cell responsible for undifferentiated vascular endothelial cells by their character and aggressiveness. The facts that antiangiogenesis suppresses arthritis and that angiotensin II is an angiogenic factor are in excellent keeping with that proposition.

Letters to the editor

Endothelium damage and von Willebrand factor antigen

Sirs: We read with great interest the recent paper by Blann et al on damage to the endothelium in Sjögren’s syndrome. The authors examined the relation of the autoantibodies SSA and SSB to endothelial damage using serum levels of von Willebrand factor antigen (vWF:Ag) as an index of damage to the endothelium. Damage of the endothelium may be present in Sjögren’s syndrome, but there is no real evidence whether such damage results in high or low levels of vWF:Ag. The extent of the production of vWF:Ag in megakaryocytes in Sjögren’s syndrome and other diseases is unknown; mainly because immunity to various antigens of the factor do not follow changes in the numbers of thrombocytes in peripheral blood and so this production site is no longer a part of the scavenger. Further, in our opinion, endothelium damage cannot explain why in increased concentrations of vWF:Ag are present in such varied diseases as proliferative glomerulonephritis, diabetes mellitus, systemic scleroderma, Sjögren’s syndrome, and arteritis temporalis, as endothelial damage in these diseases is not a common denominator.

Arthritis and carcinoma

Sirs: We read with interest the paper by Chakravarty and Webley describing two cases of asymptomatic renal cell carcinoma causing an acute monarthritis, previously unreported. They suggested that this occurrence is both rare and underreported. In our experience this is not necessarily the case. We have recently seen two patients whose cases illustrate some interesting similarities.

Patient No 1, a 63 year old man presented to our hospital with a five week history of pain in the left knee and was unable to bear weight. Clinical examination confirmed an acute monarthrosis of the knee joint, with a tense effusion, warmth, and tenderness. He had received treatment for a large cell solid tempor-orbital tumour by radiotherapy because the lesion was considered inoperable. The knee joint effusion was aspirated to rule out sepsis. Bacteriology was negative, no crystals were found, but adenocarcinoma cells were seen in abundance. He made an excellent functional recovery after palliative irradiation to the knee.

Patient No 2, a 63 year old woman, was referred to the radiotherapy department of the same hospital with metastatic disease for which no primary tumour had been located despite extensive investigation. She had initially presented with a painful knee of one year’s duration. Clinical examination showed an acute monarthritis with a moderate effusion. Isotope bone scan disclosed a hot spot in the upper tibia. She had a synovial biopsy and cytological examination of the synovial fluid. The synovial biopsy sample showed evidence of infiltration with adenocarcinomatous cells as did the synovial fluid.

While we agree with the authors that in cases where there is doubt about the cause of a joint effusion, early examination of synovial fluid is important, and may prevent the need for an open or closed bone biopsy, we are of the opinion that the occurrence of malignant joint effusions is not rare but more likely to be underreported.


References


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It may be useful to re-evaluate the role of macrophages in rheumatoid arthritis in the light of the new knowledge about the transdifferentiation of vascular endothelium. For example, the mesenchymal transformation cell responsible for joint destruction differentiates into fibroblasts in due course and are not, therefore, inflammatory cells. McCachen considers, however, any collagenase producing cells immuno-competent with Leu-M3 or HAM56 to be macrophages. Again, these antibodies are not macrophage specific and cross react with vascular endothelial cells. It is mesenchymal transformation cell responsible for undifferentiated vascular endothelial cells by their character and aggressiveness. The facts that antiangiogenesis suppresses arthritis and that angiotensin II is an angiogenic factor are in excellent keeping with that proposition.
CORRESPONDENCE

Viborg, Viborg (the haematoxylin. diseases, increased myalgia As seen pattern of presence occurring are no there antigen of vWF from newv


The author's reply: Elling et al. propose that raised circulating levels of von Willebrand factor antigen (vWFAg) reflect not endothelial cell damage but production by endothelial cells in newly growing microvasculature, challenging existing dogma. In support of this hypothesis they offer an immunohisto
graphical photograph from a patient with temporal arthritis taken from a previous publication which examined temporal artery biopsy specimens from patients with tempor
apolis, polymyalgia rheumatica, and other disease. They found raised serum vWFAg and intense vWFAg staining in new vessels in the lamina elastica only in patients with arthritis temporalis, but offer no mechanism or evidence that these are 'new' vessels. Could it be that the intense staining seen in the elastic lamina is because these endothelial cells are damaged? From the photograph it is difficult to tell if all or part of the intense staining for vWFAg is from intact cells, disrupted cells, or from vWFAg in the general connective tissue stroma.

I am surprised that Elling et al. suggest that endothelial damage cannot explain why increased concentrations of vWFAg are present in such varied diseases as proliferative glomerulonephritis, diabetes mellitus, systemic sclerosis, Sjögren's syndrome, and arthritis temporalis, as endothelial damage in these diseases is not a common denominator. Other workers, such as Compi et al., have expressed an opposite view, stating that vessel injury is a common feature of scleroderma, glomerulone

There seems to be little disagreement about the presence of raised vWFAg in a large number of conditions, some of which may be characterised by histological evidence of injury to the vasculature. However, the exact mechanism, in many cases, is unclear. Raised vWFAg is common in the acute phase response, but it would be surprising if there was evidence of damaged endothelium in this condition. It may be that in this case endothelial cells are merely 'activated' or 'stimulated' to produce vWFAg in expectation of a more severe insult (i.e. septicaemia) which they thereby damage the endothelium. Further increases in vWFAg may be the product of increased synthesis by actively growing cells in the capillary beds, the adventitia, or elsewhere. If this were true then one would need to explain why there should be an extra growth of endothelial cells, or upregulated production from a resting cell. Perhaps existing cells are being damaged, possibly to the point of cell death, by a disease process, such as the combined effects of immune complexes and complement in vasculitis or ketoacidosis in diabetes. Probably the ultimate proof of injury/damage would be an electron micrograph study of the endothelium in human disease. Such work would need to show a damaged endothelial cell with absent or depleted Wisteria bodies (i.e. structures of vWFAg), ideally with immunocytochemistry for cytoplasmic vWFAg, alongside plasma levels of vWFAg. Another approach may be to look at vWFAg mRNA from in vivo 'damaged' and 'undamaged' endothelial cells—but these data would not provide information about vWFAg in Wisteria-Palade bodies.

Until such data are easily obtained then the hypothesis that raised vWFAg is produced by injured endothelial cells in vivo may never be completely accepted. Yet despite this there remains a wealth of clinical and non-clinical data from many different diseases which all support the hypothesis. Convincing competing hypotheses would need to take account of all these findings.

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There are no signs of damage to the endothelium, and have shown that intense production of vWFAg occurs in the many new vessels occurring in the inflammatory infiltrates (figure). The figure also shows the presence of vWFAg as a slight immunoperoxidase staining in endothelial cells. This staining pattern is not different from the pattern seen in normal temporal arteries or in biopsy specimens from patients with polymyalgia rheumatica and normal levels of vWFAg. As similar microvascular abnormalities (the introduction of many new vessels) are present in most of the diseases with increased vWFAg mentioned above, the reliability of raised levels of vWFAg in these diseases, including Sjögren's syndrome, as a marker of endothelial damage should be reconsidered.

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