Farmacologia Cardiovascolare dei Donatori di Ossido d'Azoto (NO): Prospettive Terapeutiche
6° Convegno Monotematico SIF – Milano, 31 Maggio 2002

NITRIC OXIDE UP-REGULATES METALLOPROTEINASES AND DOWN-REGULATES TISSUE INHIBITOR OF METALLOPROTEINASES IN VASCULAR ENDOTHELIAL GROWTH FACTOR-INDUCED ANGIOGENESIS

S. Donnini, L. Morbidelli, S. Cantara, M. Ziche
Inst. of Pharmacological Sciences, University of Siena, Via Aldo Moro 2, 53100 Siena

Matrix metalloproteinases (MMPs) and their inhibitors (TIMPS) are tightly associated with extracellular matrix (ECM) homeostasis. However, many evidences suggest that MMPs and TIMPs are multifunctional proteins, which regulate cell proliferation, apoptosis, and angiogenesis. We and others have demonstrated that nitric oxide (NO) plays a pivotal role in physiological and pathological angiogenesis.
The aim of this study has been to investigate the role of NO on the expression, activation and inhibition of gelatinases MMP-2 and MMP-9 and of their endogenous tissue inhibitors during the angiogenic response prompted by vascular endothelial growth factor (VEGF). Coronary post-capillary endothelial cells (CVEC) constitutively expressed MMP-2 and MMP-9 gelatinases. Exposure of CVEC to VEGF increased both zymogen and activated forms of MMP-2 and MMP-9. Inhibition of the cGMP-dependent NO pathway with KT5823 up-regulated TIMP-1 and TIMP-2 expression and release, blocked the activation of MMP-2, MMP-9 and inhibited VEGF induced endothelial cell functions. Consistently, a cGMP analogue down-regulated TIMP-2 and promoted gelatinase expression, cell growth and chemoinvasion.
These results demonstrate that: 1) endogenous NO production controls the angiogenic switch of the endothelium by exerting a constitutive negative control on TIMPs production, 2) inhibition of NO pathway in endothelium upregulates endogenous TIMPs, turning off VEGF-induced proteolytic activity and angiogenesis.