PATHOGENESIS OF ABDOMINAL AORTIC ANEURYSMS: THE ROLE OF METALLOPROTEINASES AND THEIR INHIBITORS

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doi:10.1136/heartjnl-2013-304019.175

An abdominal aortic aneurysm (AAA) represents a complex pathophysiological process of weakening and dilatation of the aortic wall, which is associated with atherosclerosis, a chronic inflammatory response and hemodynamic alterations. Degradation of the extracellular matrix by the matrix metalloproteinases (MMPs) and an imbalance between MMPs and their tissue inhibitors (TIMPs), as well as the production of reactive oxygen species, have fundamental roles in the development of AAA. The exact pathogenetic mechanisms remain incompletely elucidated. In this study, we used an experimental model that was developed in our laboratory to induce AAA by combining two potential causes of MMP secretion: inflammation and turbulent blood flow. Male Wistar rats were divided into a control group (C) and an aneurysm group (A). The rats in group A received both an injury and extrinsic stenosis of the wall of the abdominal aorta. The rats in group C received a sham operation. The rats were euthanized at 3, 7 or 15 days post-surgery (dps). Sections of the aorta including the aneurysm were collected for morphological studies and MMP-2 and -9 and TIMP-1 and -2 assays. Dilatation to more than 300% of the normal aortic diameter was observed on 3 dps in 65% of the rats in group A and was similar at 7 and 15 dps. The AAA wall underwent an intense remodeling process characterized by a severe inflammatory response (neutrophils, macrophages and lymphocytes), considerable destruction of elastin fibers and deposition of collagen as well as an increase in the myofibroblast population and neovascularization. These alterations were directly related to the dramatic increase of the levels of MMP-2 and -9 and TIMP-1 and -2 throughout the study period. Immunohistochemistry revealed an increase in the level of inducible nitric oxide synthase (iNOS) in A group rats, suggesting that reactive oxygen species (ROS) contribute to the degeneration of the aortic wall. AAA results from a cascade of events that culminate in dilatation of the aortic wall. The inflammatory process associated with turbulent intraluminal flow most likely causes endothelial dysfunction that creates a milieu favorable to the release of MMPs. The MMPs cause massive destruction of elastin fibers which significantly remodels the arterial wall, resulting in dilatation and AAA formation. Reactive oxygen species play a role in the development of aneurysms. Increasing the levels of TIMPs, proportional to the increased levels of ROS, was not sufficient to block the formation of AAA. Further studies are being conducted to elucidate the role of inflammatory cells and turbulent blood flow in the pathogenesis of AAAs in this experimental model.