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Expression of Inducible Nitric-Oxide Synthase in Human Abdominal Aortic Aneurysms and its role in Programmed Cell Death

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Nitric Oxide (NO), derived from the oxidation of L-arginine catalyzed by inducible NO synthase (iNOS), has been shown to play an important part in vascular physiology and pathology. Previous investigations have showed that abdominal aortic aneurysms (AAA) tissue has a significantly elevated concentration of nitrite ion, and inhibition of iNOS limits nitric oxide production and aneurysm expansion. Transfection of vascular SMCs using iNOS cDNA showed that a large generation of NO derived from iNOS overexpression led to a marked apoptosis in vascular SMCs. These evidences suggest that NO may play a part in aneurysm pathogenesis. However, till now, the identification of iNOS expression in human AAA tissue is still not defined, and previous researches are largely based on the indirect evidence from other vascular diseases. Our present study was aimed to detect the expession of iNOS in association with the cell type and simultaneously detect the presence and distribution of apoptosis in AAA.

We obtained Human AAA specimen from patients undergoing elective repair (n=25) in the operating room, Normal aortic specimens were obtained from normal organ transplant donors (n=4) and at autopsy (n=6), subjects have no evidence or medical history of aneurysmal or occlusive disease. We used iNOS DNA oligonucleotide probe to detect iNOS mRNA expression by in situ hybridization, and combined with immunohistochemical staining with anti-SMC actin, anti-CD3, anti-CD20, or anti-CD68 antibodies at the same sections to detect its cellular localization. Tissue sections were immunostained with anti-iNOS and anti-nitrotyrosine antibodies to confirm the iNOS protein expression and presence of nitrated proteins. We used TUNEL combined with immunohistostaining of anti-SMC actin, anti-CD3, anti-CD20, or anti-CD68 antibodies to detect the presence of apoptosis and its cell type.

In situ hybridization showed that iNOS mRNA expressed in T, B Lymphocytes, Macrophages and SMCs in media and adventitia of AAA. Immunohistochemistry confirmed the presence and distribution of iNOS and nitrotyrosine in AAA, which was in accordance with that of iNOS mRNA. TUNEL staining revealed that there were elevated apoptotic markers in AAA compared with normal aortic tissues, and most of these markers were located in SMCs and macrophages.

Therefore, we conclude that in human AAA there is a constant leukocytic infiltration, a lack of SMC along with reduced elastic fibers. iNOS mRNA and protein are strongly expressed in human AAA, where they are associated with extensive nitration of tyrosine. NO probably functions as pro-apoptotic and anti-apoptotic factor in the development of AAA. Lymphocytes invading into the aortic wall are protected against apoptosis while SMCs undergo progressive programmed cell death. Besides NO has a direct destructive effect to elastin and promotes neovascularization, underlining its important role in the pathogenesis of AAA.