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Histone citrullination of neutrophil extracellular traps is a novel biomarker and target to inhibit progression of abdominal aortic aneurysms

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Background: Neutrophil extracellular traps (NETs) have been implicated in the pathogenesis of abdominal aortic aneurysms (AAAs). NET formation involves histone modifications such as citrullination allowing for DNA decondensation and DNA release into extracellular space. NETs have been detected in the adventitia and intraluminal thrombus (ILT) of AAAs and the associated proteins have been proposed to promote the inflammatory reaction that drives aneurysm development.

Purpose: Our study has addressed the notion that NET components might serve as AAA biomarkers or novel targets of AAA therapy.

Methods: Parameters of neutrophil activation as well as NET formation were determined in blood and tissue samples collected from 40 AAA patients (scheduled for surgical repair) and 40 healthy controls matched for age, sex, body mass index and smoking habit. Neutrophil and NET components were determined by ELISA in patient plasma or conditioned medium of resected tissue. NETs were visualised in aortic wall and ILT by immunofluorescence microscopy. In a model of AAA formation based on angiotensin II administration to ApoE null mice, inhibition of NET formation was tested by applying a citrullination blocker.

Results: Among the tested parameters of neutrophil activation and NET formation, citrullinated histone H3 was found to be significantly increased in blood (median 362 vs. 309 ng/ml; p=0.004) and aortic tissue (50.9 vs. 3.7 ng/mg; p=0.001) of AAA patients compared to healthy controls. Furthermore, NETs were highly prevalent in the intraluminal thrombus (corresponding to 642.3 ng citrullinated histone H3 per mg ILT). Plasma levels of citrullinated histone H3 decreased significantly after surgical repair. *In vivo* application of a citrullination inhibitor significantly reduced the capacity of mouse neutrophils to undergo NET formation. Furthermore, when aneurysm formation was initiated by angiotensin II application, disease progression was prevented in mice treated with the NET inhibitor (N=5) as compared to controls (N=5; p=0.014).

Conclusions: Histone citrullination which occurs during the formation of neutrophil extracellular traps was revealed as a biomarker of AAA formation and a potential therapeutic target to control aneurysm progression in established disease (as would be required for clinical application).