Abstract: P152

The Q222R deoxyribonuclease I single nucleotide polymorphism is associated with mortality in patients after ST-elevation myocardial infarction

Authors:
A Ondracek¹, TM Hofbauer¹, T Scherz¹, J Mueller¹, A Panzenboeck¹, A Mangold¹, IM Lang¹, ¹Medical University of Vienna - Vienna - Austria,

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Background

Neutrophils are able to release their nuclear content into extracellular space by formation of neutrophil extracellular traps (NETs). NETs are capable to neutralize pathogens, but have also been implicated in autoimmune and thrombotic diseases, including ST-elevation myocardial infarction (STEMI). Deoxyribonuclease (DNase) I degrades NETs. DNase I Q222R single nucleotide polymorphism (SNP), which impairs DNase I function, was associated with an increased incidence of MI. In STEMI, impaired DNase I activity was correlated with increased NET burden and infarct size. In a mouse model of coronary artery ligation, DNase I treatment decreased infarct size, indicating a potential therapeutic role.

Purpose

We hypothesized that DNase I is crucial to counteract dysregulated NET formation in coronary artery disease (CAD). The Q222R SNP in the DNase I gene, resulting in dysfunction of the enzyme, might thereby induce chronic NET burden with influence on long-term outcome.

Methods

We enrolled CAD patients with a history of STEMI which received primary percutaneous coronary intervention between 2006 and 2016 (n=711). Genotyping using allelic discrimination qPCR was performed to identify DNase I Q222R SNP (rs1053874). Mortality data was obtained from the national registry of death. Causes of death were classified according to ICD-10. By multivariable Cox regression, we assessed the influence of DNase I SNP on all-cause and cardiovascular mortality, adjusting for the following established cardiovascular risk factors: age, sex, body mass index, diabetes, smoking, hyperlipidemia, renal function as measured by serum creatinine concentration at admission and arterial hypertension.

Results

Homozygous mutation of the DNase I SNP was present in 64 (9.0%) patients; 304 (42.8%) and 343 (48.2%) were heterozygous and homozygous for the wild-type allele, respectively. Median survival was 60.0 [interquartile range 30.3; 91.5] months. A total of 133 (18.7%) patients deceased; 78 (11.0%) died of cardiovascular causes. Homozygous mutation of DNase I was independently associated with all-cause mortality (hazard ratio 2.05, 95% CI 1.22-3.46, p=0.006) and cardiovascular mortality (hazard ratio 2.02, 95% CI 1.02-4.01, p=0.046).

Conclusion

We report a negative influence of the Q222R DNase I SNP on survival after STEMI. Our findings argue for a
deleterious role of NETs not only in CAD.