The display of pro-thrombotic phenotype of mice carrying the BDNF Val66Met human polymorphism is prevented by treatment with Resveratrol

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Recently, large prospective studies have strongly established a connection between cardiovascular diseases (CVDs) and mood disorders, including depression. The mechanisms underlying these pathological conditions are not well identified. Neurotrophins, key mediators in neuronal maintenance and depressive disorders, play also a critical role in physiological and pathological processes in cardiovascular system. The impact of single nucleotide polymorphism in the BDNF gene (BDNFVal66Met), previously associated with depression, on CVD is not well understood, and, no information is available about its effect on thrombosis. In this study, we have investigated in an animal model whether and how BDNF Val66Met polymorphism predisposes to thrombosis.

Homozygote knock-in mouse carrying the BDNF Val66Met human polymorphism ($BDNF^{Met/Met}$) showed concomitantly depressive like and pro-thrombotic phenotype. Induction of carotid artery thrombosis by Ferric Chloride application, promoted a faster and greater thrombus formation in $BDNF^{Met/Met}$ compared to WT mice. The predisposition to thrombosis of mice expressing Met allele was also supported by their hyper-coagulable state and by increased platelets reactivity. In addition, higher amounts of TF and lower levels of deacetylase SIRT-1 have been detected in aorta tissues of $BDNF^{Met/Met}$ mice.

Pharmacological activation of SIRT-1 by Resveratrol rescued the prothrombotic phenotype in homozygote knock-in mouse. In particular, it prevented thrombus formation and restored the physiological levels of coagulation and platelet activation markers (e.g. functional fibrinogen, plasma TSP-1 and gelsolin, TF expression/activity in microparticles, aorta tissue and circulating leukocytes, and platelets-leukocytes aggregates). In addition, activation of SIRT1 decreased the number of circulating platelets and leukocytes only in mouse carrying the BDNF Val66Met polymorphism.

In conclusion, the present study shows that BDNF Val66Met polymorphism predisposes to thrombotic status and that Resveratrol treatment reverts this phenotype in mice. Modulation of SIRT-1 may offer novel therapeutic options for targetingthrombosis in patients affected by depression.