Carbaprostacyclin prevents venous thrombosis in COX-2 KO mice: the new role of monocytes

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Deep vein thrombosis (DVT) is a serious national health problem, and despite appropriate therapy, pulmonary thromboembolism, represents the most common complication that leads to death 1,2. Innovative therapeutic approaches and elucidations about mechanisms involved in this pathology are needed.

The Cyclooxigenase enzymes (COX-1 and COX-2) are involved in intercellular communication, tissue homeostasis and gastrointestinal protection, and play a critical role in arterial thrombosis, whereas their impact in venous thrombosis (VT) is still unclear. In particular, meanwhile it is well known that COX-1 inhibition reduces the incidence of VTE3,4, the role of COX-2 on this pathology is under debate.

The aim of this study is to assess the impact of COX-2 deletion in venous thrombosis focusing on the effect of prostacyclin in this experimental setting.

Deletion of COX-2 reduced levels of both the PGI2 metabolite 2,3-dinor-6ketoPGF1α (PGIM) in urine and 6-keto-PGF1α in carotid rings and predisposed to venous thrombosis as suggested by the increased number of platelet-monocyte aggregates and provided by formation of bigger thrombi after inferior vena cava ligation.

Venous thrombi from COX-2KO mice showed the higher number of infiltrated monocytes/macrophages, and of tissue factor (TF) positive cells compared to WT.

Surprisingly, Annexin A2 (ANXA2), a key modulator of fibrinolysis5 and putative regulators of TF expression6, was higher in thrombi of mutant mice, and it was expressed preferentially in the cytosol and into the nucleus of intrathrombus-cells, while in WT thrombi was localized on cells surface and into the cytosol.

Interestingly, administration of Carbaprostacyclin, a stable analogue of prostacyclin, reduced markedly the percentage of circulating platelet-monocyte aggregates, and the number of monocytes as well as the TF+ and ANXA2+cells in venous thrombi, and decreased dramatically the thrombus size in COX-2KO mice. This treatment did not affect the composition and the size of WT venous thrombi. Remarkably, depletion of monocytes with gadolinium completely prevented venous thrombus growing only in mutant mice, suggesting a critical role of COX-2KO monocytes in this experimental setting.

Of relevance, in line with the data of venous thrombus, circulating monocytes from COX-2KO mice presented higher TF activity and lower membrane expression of ANXA2 and greater accumulation of ANXA2 into the nucleus compared to WT.

COX-2KO peritoneal macrophages, used as surrogate of monocyte/macrophages present in venous thrombi, showed greater TF activity and higher expression of ANXA2. Interestingly, COX-2 deletion induced the assembly of ANXA2/p50NF-kB complex and promoted the trafficking of ANXA2 and p50NF-kB into the nucleus. Finally, the treatment of carbaprostacyclin restored the physiological distribution of ANXA2 at membrane and cytosol level and prevented TF activation in COX-2KO macrophages.

In conclusion, our data, disentangling the mechanism(s) by which COX-2 deletion affect venous thrombosis, provide a possible explanation of higher VT risk exacerbated by COXIBs and suggest the importance of monocytes not only in later thrombus resolution but also in early thrombogenesis. Further, these data are of clinical relevance in proposing those strategies aimed at increasing PGI2 that might help to prevent venous thrombosis affecting ANXA2/TF pathway in monocytes.

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