Endothelial P2X7 promotes venous thromboembolism

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Résumé

Background: Venous thromboembolism (VTE) affects 117 people per 100,000 each year and is an important cause of morbidity and mortality. VTE can lead to 1) death through pulmonary embolism, 2) the post-thrombotic syndrome, or 3) pulmonary sequelae that dramatically impair quality of life. Thrombosis has long been characterized by the Virchow’s triad encompassing hypercoagulability, venous stasis and vascular wall damage. However, inflammatory pathways are now well recognized mechanisms involved in the physiopathology of venous thromboembolism. Endothelial cells play critical roles in regulating immune functions in response to PAMPs and DAMPs. During inflammation, adenosine triphosphate (ATP) is released in the extracellular compartment and is recognized as a danger signal by endothelial cells. ATP can interact with the CD39/CD73 system involved in the metabolism of ATP into AMP. Recent data indicated that the CD39/CD73 system might protect against venous thrombosis by downregulating the NLRP3 inflammasome. ATP can also interact with the P2X7 receptor involved in a wide range of responses including NLRP3 inflammasome activation leading to IL1β production.

Aims: To determine how the endothelial P2X7 receptor contributes to venous thromboembolism.

Method: After pretreatment with TNFa, HUVECs were incubated with BzATP alone or with thrombin. Immunofluorescence, western blot and real-time quantitative PCR analyses were used to study P2X7 expression in endothelial cells, activation of p38 and NFκB signaling pathways and gene expression, respectively. The P2X7 expression was also study in in vivo model.

Results: We confirmed that HUVECs expressed P2X7 receptor in vitro and in vivo after induction of venous thrombosis in an experimental model. BzATP and thrombin induced the activation of p38 and NFκB signaling pathways. Interestingly, the TNF priming is associated with an increase of NLRP3 and IL1b expression. There expressions are observed in ARN and in protein. In addition, ICAM-1 and VCAM-1 expression was increased, while thrombomodulin expression was decreased. We also discuss of the P2X7 impact on the thrombus composition and size in P2X7 -/- mouse.

Summary/Conclusion: Our data suggest that ATP released in the extracellular space during venous thrombosis induced inflammasome activation in endothelial cell through P2X7 activation. P2X7 might have a pro-thrombotic role exacerbating venous thromboembolism.

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