CARDIOVASCULAR DISORDERS

Resolving blood clots

Current therapies for deep vein thrombosis (DVT) — which can occur as a result of immobilization, surgery and pregnancy — such as heparins, warfarin and the new-generation anticoagulants act on the coagulation cascade rather than directly targeting the thrombus. Now, Nosaka and colleagues show that inhibiting interferon-γ (IFNγ) can accelerate thrombus resolution in a mouse model of DVT.

As the processes that are involved in thrombus resolution resemble those that are involved in wound healing, in which the IFNγ–signal transducer and activator of transcription 1 signalling pathway is involved, the authors examined the role of IFNγ in thrombus resolution in IFNγ-deficient (*Ifng*$^{-/-}$) mice and in a mouse model of DVT induced by ligation of the inferior vena cava (IVC).

In the mouse model, IFNγ was present in macrophages that infiltrated the thrombus, and its expression increased as thrombi aged. In *Ifng*$^{-/-}$ mice, thrombi started to reduce in size 10 days after IVC ligation and were smaller in size and mass than the thrombi in wild-type mice, which suggested that the absence of IFNγ could accelerate thrombus resolution.

Matrix metalloproteinase 2 (MMP2) and MMP9 have crucial roles during thrombus resolution, and work suggested that IFNγ suppresses the expression and activity of MMP9 in macrophages that are present in the thrombus. Intrathrombotic recanalization — the formation of new vascular channels within the thrombus — is also necessary for thrombus resolution, and *Ifng*$^{-/-}$ mice had increased numbers of intrathrombotic channels and improved blood flow through the IVC region. Furthermore, intrathrombotic expression of vascular endothelial growth factor (*Vegf*) was enhanced in *Ifng*$^{-/-}$ mice. *In vitro* studies confirmed that IFNγ negatively regulated the expression of *Mmp9* and *Vegf* in macrophages.

Finally, administration of a monoclonal antibody (mAb) directed against IFNγ to mice resulted in reduced thrombus mass and increased blood flow through the thrombus, which were accompanied by increased expression of *Mmp9* and *Vegf*. Moreover, the mAb did not cause any abnormalities in coagulation function. So, this study indicates that inhibiting IFNγ could be beneficial in the treatment of DVT and possibly other thrombotic disorders.

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ORIGINAL RESEARCH PAPER Nosaka, M. *et al.* Absence of IFN-γ accelerates thrombus resolution through enhanced MMP-9 and VEGF expression in mice. *J. Clin. Invest.* **121**, 2911–2920 (2011)

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