Small Molecules: A Novel Approach to Alter Fibrinogen Production and Impact Venous Thrombosis

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Inhibition of thrombosis is one of the main targets of treatment for the prevention of cardiovascular disease (CVD) events. While a range of antithrombotics, with varying degrees of success, exists, current treatments are not without risk or limitation. The identification of novel antithrombotics remains therefore a topic of clinical importance.

Fibrinogen, a large glycoprotein, synthesized primarily in the liver, with a normal plasma concentration of 1.5 to 4.0 g/L, is the most abundant blood coagulation factor and an important role player in thrombosis.[1] Increased fibrinogen can contribute to thrombosis and CVD by increasing blood viscosity, by contributing to inflammation and atherogenesis, and by promoting thrombogenesis. Thrombogenesis itself can be mediated through increased platelet aggregation, altered fibrin clot structure, and enhanced red blood cell attachment to thrombi, rendering fibrin clots resistant to lysis.[2]

In this issue of *Thrombosis and Haemostasis*, Vilar et al used an elegant approach to identify bioactive small molecules that can modulate fibrinogen levels in human cell lines and zebrafish larvae and followed this up with functionally testing their effects on laser-induced venous thrombosis in zebrafish.[3] A total of 1,280 active compounds from a bioactive molecule library[4] were screened for their ability to alter fibrinogen production by HepG2 cells followed by a series of selection steps in additional cellular models and zebrafish larvae. Of these chemical modulators, two were identified for further study: anthralin, which decreased fibrinogen production, and all-*trans* retinoic acid (RA), which increased it. In addition to altering fibrinogen production, anthralin prolonged the time to vessel occlusion and reduced thrombocyte aggregation, while RA had opposing prothrombotic effects.

These results, together with data from experiments with a fibrinogen-targeting morpholino in which larval fibrinogen levels correlate with laser-induced thrombosis times, reinforce the notion that fibrinogen levels can directly influence venous thrombosis and highlight the potential benefit of fibrinogen-lowering therapy.

Conflict of Interest
None declared.

References

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