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POSTER ABSTRACTS

331.THROMBOSIS

The Resolution Mediator Annexin A1 Affords Protection Against Thromboinflammation

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Abstract Stroke is a leading cause of death and disability worldwide, with the majority (~85 %) being ischemic in origin. Age is the most important non-modifiable risk factor for acute ischemic stroke (AIS). While inflammation with ageing is a well-known complication of AIS, a new model is emerging in which ageing-associated thrombosis is being viewed as a multi-step, multi-cellular process driven by inflammatory stimuli and recruitment/activation of leukocytes. The ideal outcome of inflammation is resolution, an active process involving specific endogenous mediators (e.g. annexin A1 [AnxA1]) and related pathways (e.g. formyl peptide receptor-2 [Fpr2/ALX] pathway).[1,2] The development of therapies that temper inflammation and enhance resolution offer potential therapeutic strategies for the treatment and management of thromboinflammation associated with AIS. We have shown that the AnxA1 mimetic peptide AnxA1 $_{Ac2\text{-}26}$ ameliorates thrombotic responses in thromboinflammatory conditions such as Sickle Cell Disease,[3] however, the role that AnxA1 plays in age-related thrombosis is currently unknown. Here we sought to comprehensively elucidate the functional significance of targeting the AnxA1/Fpr2/ALX pathway in age-related thrombosis.

Initially, to evaluate the role of AnxA1, thrombosis in cerebral vessels was induced using the light/dye thrombosis model.[2] Male and female adult (10-14 weeks) and ageing (18-24 months) wild type (WT, C57/BL6) or AnxA1 knock-out (AnxA1 $^{-/-}$) mice were used. WT mice received AnxA1 (1 μg/mouse), or saline vehicle injected 20 min before the onset of thrombus formation in cerebral pial vessels. Thrombogenesis and blood flow cessation times were quantified. AnxA1 treatment was able to prolong blood flow cessation times in both cerebral arterioles and venules, an effect which was more pronounced in ageing mice ($p<0.05$) via regulation of the FPR2/ALX-pathway.

Next, to investigate the mechanism of action of AnxA1 in an inflammatory backdrop (i.e. lipopolysaccharide [LPS]), the effect of AnxA1 on platelet P-selectin and αIIbβ3 receptor expression, following stimulation with the GPVI collagen receptor agonist convulxin (CVX), was performed. CVX treatment increased platelet activation, which was suppressed by AnxA1 co-administration (100 ng. $p<0.05$). CVX+LPS increased platelet αIIbβ3 or P-selectin levels, which were inhibited by the administration of AnxA1.

Finally, to determine whether a deletion of *AnxA1* impacts thrombosis, we performed the light/dye thrombosis model in AnxA1 $^{-/-}$ mice. These mice displayed accelerated cerebral microvascular thrombus formation (decrease in blood flow cessation time) compared to WT mice in both arterioles and venules (arterioles: 17.9 ± 2.3 vs 33.2 ± 1.9 min and venules: 13.2 ± 2.4 vs 20.9 ± 2.2 min. $p<0.05$).

In conclusion, these results demonstrate the ability of AnxA1 to modify the thromboinflammatory environment, including reducing platelet activation under inflammatory conditions *via* GPVI. Collectively, these data show the importance of the AnxA1/Fpr2/ALX system in effecting the resolution of cerebral thromboinflammation in ageing and may provide a novel therapeutic strategy for AIS and other thromboinflammatory conditions.

Disclosures No relevant conflicts of interest to declare.

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