The Annexin A1-Formyl Peptide Receptor 2 Pathway Regulates Cerebral Thrombo-inflammation

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Sickle Cell Disease (SCD) is a devastating lifelong genetic disease which affects multiple individuals worldwide. In particular, patients with SCD are more susceptible to thrombotic events, although the underlying mechanisms promoting a pro-thrombotic and pro-inflammatory phenotype in SCD remain largely unknown (especially in the brain). The causes for the SCD phenotype may however relate to a well-established link between thrombosis and inflammation i.e. inflammation can beget local thrombosis, and thrombosis can amplify inflammation.

We have focused on the anti-inflammatory and pro-resolving endogenous mediator Annexin A1 (AnxA1) and its interaction with the Formyl Peptide Receptor (FPR) family. Of relevance, both AnxA1 and lipoxin A4 (LXA4/ATL) mediate their effects through a one specific member of the FPR family, that being FPR2 (also called lipoxin A4 receptor [ALX]). Here we have tested the effect of targeting the AnxA1-FPR2/ALX pathway as a therapeutic strategy for SCD with a special focus on thrombo-inflammation. We present novel evidence for a previously unknown role of the AnxA1-FPR2/ALX system in effecting the resolution of SCD associated cerebral thrombo-inflammation.

In summary, the AnxA1-FPR2/ALX system is a potential therapeutic target for initiating endogenous anti-thrombo-inflammatory and pro-resolving pathways in SCD.