Pharmacological targeting of bioactive lipid production improves experimental lymphatic filariasis pathology

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Abstract:

Lymphatic filariasis (LF) is a Neglected Tropical Disease prioritised for global elimination, one of the main aetiological agents of non-hereditary lymphoedema and a major cause of global disability. An estimated 36 million individuals with LF infections worldwide suffer stigmatising chronic morbidities (elephantiasis or hydrocoele) which can drive depressive illness. The current LF elimination strategy by mass drug administration of standard anti-filarial drugs has negligible impact at moderating pre-established lymphatic disease. However, long-courses of high dose doxycycline treatment have shown promising results in reversing early lymphoedema grade in phase II clinical trials, demonstrating proof-of-concept that filarial pathology can be pharmacologically targeted. Our recent research has shown that in LF laboratory models, the anti-morbidity mechanism of doxycycline is via targeting a type-2 adaptive immune-mediated inflammatory pathway responsible for triggering lymphangiogenesis, aberrant lymphatic vessel formation, dilatation and lymphatic insufficiency. In other secondary lymphoedemas, emerging evidence implicates eicosanoid lipid inflammatory mediators in disease progression. Here, using an established murine experimental hind-limb model of *Brugia malayi* infection, we evaluated the role of eicosanoids in LF lymphatic pathology. The cyclooxygenase-(COX)2 and lipoxygenase(LOX)5 terminal metabolites, prostaglandin(PG)E2 and leukotriene(LT)B4 were significantly upregulated in circulation of *B. malayi* infected mice and were modulated following effective anti-morbidity doxycycline treatment. Both eicosanoids directly stimulated lymphatic endothelial cell proliferation *in vitro.* We therefore investigated the effect of COX/LOX pharmacological inhibitor treatment on lymphatic structure and function in *B. malayi* infected mice using near-infrared (NIR) intravital indocyanine green (ICG) lymphography. COX/LOX inhibitor treatment significantly decreased lymphatic remodelling in dorsal, lateral, and ventral aspects of

the infected limb compared to vehicle treated animals. These initial results uncover the novel potential of targeting bioactive lipid pathways with affordable and safe non-steroidal anti-inflammatory drugs for the treatment of filarial lymphatic disease.