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Authors(s)	Reynolds, Alison; Fernandez, Jessica Garcia; Osman, Janina; Ventosa, Pilar; Fernandez, Yolanda; Sjölander, Anita; Kennedy, Breandán
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ARVO Annual Meeting Abstract | September 2016

Investigation of the role of cysteinyl leukotrienes in ocular developmental angiogenesis.

[Alison L Reynolds](#); [Jessica Garcia Fernandez](#); [Janina Osman](#); [Pilar Ventosa](#); [Yolanda Fernandez](#); [Anita Sjölander](#); [Breandan N Kennedy](#)

Abstract

Purpose : Previously, we identified quininib (2-[(*E*)-2-(quinolin-2-yl)vinyl] phenol) and a related series of cysteinyl leukotriene (cysLT) receptor antagonists which inhibit hyaloid vessel development in zebrafish eyes. Here, we more comprehensively characterise the expression and function of specific cysLT signalling components in ocular developmental angiogenesis.

Methods : More than 40 analogues of the cysLT receptor antagonist, quininib, were synthesised. Anti-angiogenic activity of each compound was ranked based on inhibition of hyaloid vessel formation in Tg[*fli1*:EGFP] zebrafish eyes. cysLT receptor antagonism was quantified using reporter cell bioassays. Inhibition of mammalian developmental retinal angiogenesis was determined by sub-cutaneous delivery of quininib in postnatal day (P)1 pups with quantification of retinal vasculature at P4 and P8. The requirement of cysLT receptors for retinal angiogenesis is being assessed in cysLT₁R and cysLT₂R knockout mice. An assessment of the spatial and temporal expression of cysLT receptors in developing mouse eyes will be performed by Western blot and immunohistochemistry.

Results : Nine quininib analogues inhibit hyaloid vasculature development equal to or greater than the parent compound. Seven quininib analogues significantly inhibited leukotriene D4 activation of CysLT₁R and enhanced inhibition of CysLT₂R activation compared to quininib. In a pilot study, 50 mg/kg quininib (n = 4) inhibited developmental retinal angiogenesis in mice by 20% compared to vehicle injected controls (n = 3; p-val =0.024). Preliminary results from *Cysltr1* and *Cysltr2* knockout mice (N = 3/group) suggests *Cysltr2* knockouts show 20% delay in retinal vascular formation.

Conclusions : Cysteinyl leukotriene signalling regulates ocular developmental angiogenesis. The cysteinyl leukotriene pathway is a therapeutic target for inhibiting aberrant pathological angiogenesis which occurs in age-related macular degeneration and diabetic retinopathy.

This is an abstract that was submitted for the 2016 ARVO Annual Meeting, held in Seattle, Wash., May 1-5, 2016.