AB033. Implication of beta-adrenergic receptor in choroidal neovascularization

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Background: We investigated the role of beta-adrenergic receptor (B-AR) on choroidal neovascularization (CNV) in an animal model of age-related macular degeneration in mice.

Methods: The angiogenic effect of the B-AR was evaluated in retinal pigment epithelium (RPE)-choroid explants from C57Bl6 mice stimulated with propranolol or isoproterenol (10 µM) (respectively antagonist and agonist of the B-AR) during 24 h. Conversely, a classic choroidal neovascularization (CNV) model induced by laser burn in C57Bl6 mice (8 weeks) was used to assess the anti-angiogenic effect of propranolol. In this experiment, mice were treated with intraperitoneal propranolol (6 mg/kg/d) or vehicle (saline solution) daily for 10 days, starting on day 4 after laser burn and until sacrifice (day 14). Immunostaining analysis on retinal flatmounts and cryosections were performed to determine the surface of CNV, the distribution of B-AR and the number and morphology of microglia/macrophages associated with CNV. To explore if the antiangiogenic effect of propranolol involved the modulation of the inflammatory microenvironment associated with CNV, we used RPE primary cells, J774 macrophages cell line and polarized M1 and M2 bone marrow-derived macrophage (BMDM). Choroidal explants treated with conditioned media (CM) from J774 or polarized M1/M2 BMDM pre-treated with propranolol to confirm the anti-angiogenic effect of propranolol. Expression of angiogenic factors was evaluated by RT PCR and Elisa.

Results: The expression and distribution of the B-1, B-2 and B-3 adrenergic receptors were localized in the choroid and RPE cells. The stimulation of RPE-choroid explants with isoproterenol increased CNV compared to vehicle, while propranolol decreased CNV. *In vivo*, propranolol inhibited significantly the levels of VEGF and CNV growth in laser burn model compared to the vehicle. Additionally, the treatment with propranolol decremented the number of activated (amoeboid shape) microglia/macrophages but surprisingly, the number of non-activated microglia/macrophages around the CNV was higher than with the vehicle treatment. *In vitro*, propranolol modulated the angiogenic balance in macrophages promoting anti-angiogenic factors expression, especially with M2 BMDM. CM from macrophages pre-treated with propranolol reduced CNV on choroidal explants.

Conclusions: These *ex vivo* and *in vivo* studies highlight the importance of B-adrenergic receptor in the CNV. Propranolol can inhibit CNV by decreasing the levels of VEGF and modulating microglia/macrophages activation. Further work will investigate the role of B-adrenergic receptor on suppression of the inflammatory environment in order to understand the link between neovascularization and inflammation in CNV during age-related macular degeneration.

Keywords: Choroidal neovascularization (CNV); macrophages; beta-adrenergic receptor (B-AR)

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