Rapamycin and Resveratrol Modulate the Gliotic and Pro-Angiogenic Response in Müller Glial Cells Under Hypoxia

Subirada, Paula V., Vaglienti, María V., Joray, Mariana Belén

, Paz, María C., Barcelona, Pablo F. and Sánchez, María C. (2022) *Rapamycin and Resveratrol Modulate the Gliotic and Pro-Angiogenic Response in Müller Glial Cells Under Hypoxia.* Frontiers in Cell and Developmental Biology, 10. ISSN 2296-634X

Resumen

Hypoxia and hypoxia-reoxygenation are frequently developed through the course of many retinal diseases of different etiologies. Müller glial cells (MGCs), together with microglia and astrocytes, participate firstly in response to the injury and later in the repair of tissue damage. New pharmacological strategies tend to modulate MGCs ability to induce angiogenesis and gliosis in order to accelerate the recovery stage. In this article, we investigated the variation in autophagy flux under hypoxia during 4 h, employing both gas culture chamber (1% O2) and chemical (CoCl2) hypoxia, and also in hypoxia-reoxygenation. Then, we delineated a strategy to induce autophagy with Rapamycin and Resveratrol and analysed the gliotic and pro-angiogenic response of MGCs under hypoxic conditions. Our results showed an increase in LC3B II and p62 protein levels after both hypoxic exposure respect to normoxia. Moreover, 1 h of reoxygenation

after gas hypoxia upregulated LC3B II levels respect to hypoxia although a decreased cell survival was observed. Exposure to low oxygen levels increased the protein expression of the glial fibrillary acid protein (GFAP) in MGCs, whereas Vimentin levels remained constant. In our experimental conditions, Rapamycin but not Resveratrol decreased GFAP protein levels in hypoxia. Finally, supernatants of MGCs incubated in hypoxic conditions and in presence of the autophagy inductors inhibited endothelial cells (ECs) tubulogenesis. In agreement with these results, reduced expression of vascular endothelial growth factor (VEGF) mRNA was observed in MGCs with Rapamycin, whereas pigment epithelium-derived factor (PEDF) mRNA levels significantly increased in MGCs incubated with Resveratrol. In conclusion, this research provides evidence about the variation of autophagy flux under hypoxia and hypoxia-reoxygenation as a protective mechanism activated in response to the injury. In addition, beneficial effects were observed with Rapamycin treatment as it decreased the gliotic response and prevented the development of newly formed blood vessels.

TIPO DE DOCUMENTO: Artículo

DOI: https://doi.org/10.3389/fcell.2022.855178

PALABRAS CLAVE: Angiogénesis. Autofagia. Hipoxia. Hipoxia-reoxigenación.

TEMAS: Q Ciencia > Q Ciencia (General)

Q Ciencia > QD Química

UNIDAD ACADÉMICA: Universidad Católica de Córdoba > Facultad de Ciencias Químicas