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Lipase involvement in the retina-protective activity of PEDF

S. Patricia Becerra
National Eye Institute, USA

Abstract

Pigment epithelium-derived factor (PEDF), a multifunctional regulatory protein in the eye, is a natural component of the interphotoreceptor matrix, vitreous and aqueous humor. It has potent retinal survival and antiapoptotic activities, and it also inhibits ocular angiogenesis. Although PEDF is a serpin member, its remarkable biological activities do not depend on its serine protease inhibitory potential, and elucidation of its molecular mechanism of action has become of great interest. We have identified the *PNPLA2* gene product, termed PEDF-R, as a lipase in plasma membranes of retina cells that has affinity for PEDF. PEDF binding stimulates the PEDF-R phospholipase activity to release fatty acids and lysophosphatidic acid. To investigate whether PEDF-R is a receptor for PEDF, we used siRNA to selectively knockdown PEDF-R in retina cells and found that PEDF-R was essential for PEDF-mediated cell survival and antiapoptotic activities. To map a functional PEDF-R ectodomain, recombinant polypeptide fragments and synthetic peptides were used in structure-function studies. A PEDF-binding region identified in PEDF-R was critical for the PEDF-mediated stimulation of the phospholipase activity. In addition, peptides derived from this region blocked the interactions between PEDF and PEDF-R, and hindered the retinal survival activities triggered by PEDF. These findings established that PEDF-R is a receptor of PEDF and contains a functional ectodomain for ligand interaction and enzymatic stimulation that is critical for retina survival activities. Our data suggested that upon binding to PEDF-R, PEDF can stimulate the release of prospective bioactive lipid mediators for action in the retina homeostasis.

Biography

S. Patricia Becerra received a Doctorate degree (Major in Biochemistry) from the University of Navarra, Spain. Her postdoctoral training was in biochemistry at the National Cancer Institute, and in molecular virology at the National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD. Becerra is head of the Section of Protein Structure and Function, Laboratory of Retinal Cell and Molecular Biology, National Eye Institute, NIH. She is an author of more than 70 peer-reviewed articles, reviews and book chapters. She serves as an editorial board member and reviewer of several journals in biochemistry, molecular biology and ophthalmology.