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Research Interests:

Synaptic signaling in neuronal plasticity and neuroprotection; oxidative stress and neuronal retinal cell survival

Selected Publications:

1. Mukherjee PK, Marcheselli VL, Barreiro S, Hu J, Bok D, **Bazan NG**. Neurotrophins enhance retinal pigment epithelial cell survival through neuroprotectin D1 signaling. Proc. Natl. Acad. Sci. USA. 104 (2007) 13152-13157.
2. Mukherjee PK, Marcheselli VL, de Rivero Vaccari JC, Gordon WC, Jackson FE, **Bazan NG**. Photoreceptor outer segment phagocytosis attenuates oxidative stress-induced apoptosis with concomitant neuroprotection D1 synthesis. Proc. Natl. Acad. Sci. USA 104 (2007) 13158-13163.
3. **Bazan NG**. Cell survival matters: docosahexaenoic acid signaling, neuroprotection and photoreceptors. Trends Neurosci. 29 (2006) 263-271.
4. Cole-Edwards KK, Musto AE, **Bazan NG**. JNK activation responses induced by hippocampal kindling are mediated by reactive astrocytes. J. Neurosci. (2006) 8295-8304.
5. Lukiw WJ, Cui JG, Marcheselli VL, Bodker M, Botkjaer A, Gotlinger K, Serhan CN, **Bazan NG**. A role for docosahexaenoic acid-derived neuroprotection D1 in neural cell survival and Alzheimer disease. J Clin Invest. 115 (2005) 2774-2783.
6. Mukherjee PK, Marcheselli VL, Serhan CN, **Bazan NG**. Neuroprotectin D1: a docosahexaenoic acid-derived docosatriene protects human retinal pigment epithelial cells from oxidative stress. Proc. Natl. Acad. Sci. USA 101 (2004) 8491-8496.
7. Rodriguez de Turco EB, Tang W, Tophan MK, Sakane F, Marcheselli VL, Chen C, Taketomi A, Prescott SM, **Bazan NG**. Diacylglycerol kinase ε regulates seizure susceptibility and long-term potentiation through arachidonoyl-inositol lipid signaling. Proc. Natl. Acad. Sci. 98 (2001) 4740-4745.

Omega-3 essential fatty acids modulate initiation and progression of neurodegenerative diseases

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The significance of the selective enrichment in omega-3 essential fatty acids (docosahexaenoyl - DHA-chains of membrane phospholipids, 22C and 6 double bonds) in the nervous system (e.g. photoreceptors, synaptic membranes) has remained, until recently, incompletely understood. While studying mechanisms of cell survival in neurodegenerations, we discovered a docosanoid synthesized from DHA by a 15-lipoxygenase, which we dubbed neuroprotectin D1 (NPD1, 10*R*, 17*S*-dihydroxy-docosa-4*Z*, 7*Z*, 11*E*, 13*E*, 15*E*, 19*Z* hexaenoic acid). This mediator is a docosanoid because it is derived from a 22C precursor (DHA), unlike eicosanoids, which are derived from the 20 C arachidonic acid family member of essential fatty acids not enriched in the nervous system. We found that NPD1 is promptly made in response to oxidative stress and brain ischemia-reperfusion, and in the presence of neurotrophins. NPD1 is neuroprotective in experimental brain damage, oxidative-stress retinal pigment epithelial (RPE) cells, and in human brain cells exposed to amyloid-β peptide. Thus we envision NPD1 as a protective sentinel, one of the very first defenses activated when cell homeostasis is threatened by neurodegenerations. We provide here recent experimental examples that highlight the specificity and potency of NPD1 spanning beneficial bioactivity during initiation and early progression of neurodegenerations: 1) Photoreceptors renew membrane disks containing the phototransduction apparatus and DHA intermittently via shedding of their tips and phagocytosis by retinal pigment epithelial (RPE) cells. At the same time, new membrane disks are made at the base of the outer segments; their length remains constant and cell integrity is maintained remarkably unchanged throughout many decades. This outcome occurs in spite of the fact that the photoreceptors are in an oxidative stress-prone environment (light, high O_2 consumption, high polyunsaturated fatty acid fluxes, etc.) We show that phagocytosis of photoreceptor disks promotes via NPD1 synthesis specific refractoriness to oxidative stress-induced apoptosis in RPE cells, which in turn fosters homeostatic photoreceptor cell integrity. Disruptions of the sentinel role of NPD1 in photoreceptor renewal may participate in macular degeneration and other retinal degenerations leading to blindness. 2) In brain ischemia-reperfusion, DHA is released and used for NPD1 synthesis, thus eliciting neuroprotection. Anti-apoptotic BCL-2 family of proteins are negatively regulated, as is the arrival of leukocytes due to neurovascular unit breakdown. 3) We found that NPD1 is drastically reduced in CA1 areas from Alzheimer's patients. Thus we have explored the significance of NPD1 in cellular models that recapitulate part of the Alzheimer's pathology. Human neurons and astrocytes challenged by amyloid-β or by overexpressing APPsw (double Swedish mutation) show that NPD1 down-regulates amyloidogenic processing of amyloid-β precursor protein, switches off pro-inflammatory gene expression (TNF-α, COX-2 and B-94-TNF-α inducible pro-inflammatory element), and promotes neural cell survival. The apoptotic cascade involves mutiple checkpoints. NPD1 regulation targets upstream events of apoptosis as well as neuroinflammatory signaling, in turn promoting homeostatic regulation of cell integrity. (Supported by NIH: NINDS R01 NS046741, NEI R01 EY005121 and NCRR P20 RR016816, and by the National Foundation Fighting Blindness).