



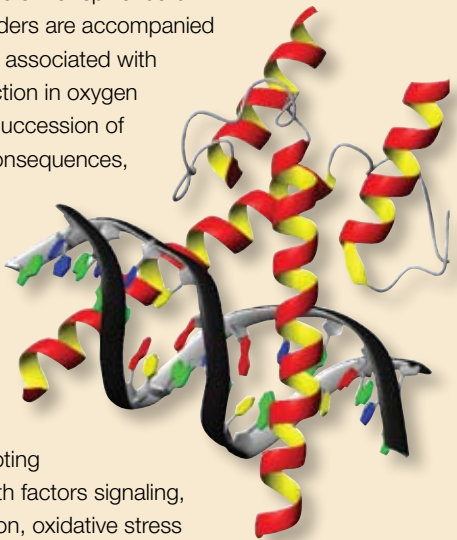
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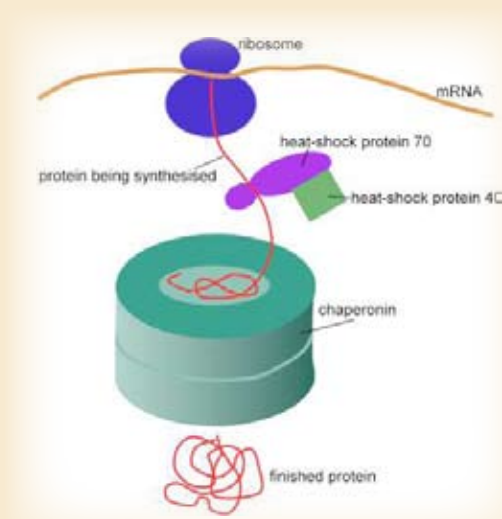
Research Activities:

Oxygen deprivation affecting cellular survival frequently occurs in cerebrovascular disorders, pulmonary diseases, sleep apnea, and nervous system injury such as brain or spinal cord traumatic injury. All these disorders are accompanied by excessive neuronal cell loss associated with sustained or intermittent restriction in oxygen supply to the neural tissue. A succession of events leads to pathological consequences, with the primary insult, followed by a secondary wave of injury mediated by various pathophysiological mechanisms, involving both necrosis and apoptosis, and expanding the primary damage. Hypoxia induces stress-related pathways promoting angiogenesis, glycolysis, growth factors signaling, genetic instability, tissue invasion, oxidative stress and apoptosis, as part of a neural tissue stress response. The balance of these pathways may determine cellular fate and disease outcome. Exposure to stress induces the expression of a highly conserved family of proteins, the heat shock proteins, a universal mechanism of cellular defense in various organisms. Constitutively expressed Hsps function as molecular chaperones and participate in protein synthesis, folding, and protein transport. During cellular stress, they play a role in preventing aggregation of damaged proteins, refolding proteins, or targeting them to degradation and may also prevent apoptosis by binding pro-apoptotic proteins and inhibiting apoptosome formation and caspase activation. Alternatively, in response to increased accumulation of misfolded or ubiquitinated proteins, Hsps can induce apoptosis to remove dysfunctional cells by releasing the bound pro-apoptotic proteins. Thus, understanding the modulation of hypoxia-induced pro- and anti-apoptotic pathways in neurons and supporting tissue, and their modulation by stress-induced proteins may provide novel therapeutic strategies for diseases involving insufficient apoptosis, such as cancer and autoimmune disease or those associated with increased apoptosis such as ischemia, neurodegenerative diseases, or traumatic injury. Therapeutic strategies interfering with the signaling events triggered in response to hypoxia/ ischemia may prevent delayed injury and improve recovery.



Various projects currently under investigation in our laboratory include:

- Cellular models in intermittent and sustained hypoxia.



- Hypoxia-induced stress response: role of heat shock proteins in the regulation of survival kinases.
- Protein-protein interactions in signaling complexes induced by hypoxia.
- Signal transduction pathways underlying cellular metabolism and adaptation to hypoxia/ischemia and oxidative stress.
- The role of stress response and heat shock protein induction in the modulation of cellular survival after spinal cord injury, and prevention of secondary traumatic injury.

Grants Funded:

Role: Principal Investigator Project 1

Title: Mechanisms of Plasticity and repair after SCI, Project 1: Heat shock proteins in spinal cord neural survival

Funding Agency: NIH/ National Center for Research Resources

Direct Costs Funded: \$ 902,020

Role: Co-Investigator

Title: Modulation of Neutrophil Apoptosis by Akt-Hsp27 Signalosome

Funding Agency: National Institute of Allergy and Infectious Diseases

Direct Costs Funded: \$ 900,000

Peer-reviewed Publications:

Machalani R, Arlotto M, Waters KA, **Gozal E**, Berger F, Dematteis M. A novel method of tissue collection and storage: Validation using SELDI-TOF MS analysis. *Clin. Chem.*53 (7): 1387-1389 (2007).

Dematteis M, Julien C, , Guillermet C, Sturm N, Lantuejoul S, Mallaret M, Levy P, **Gozal E**. Intermittent hypoxia induces Early functional and structural cardiovascular remodeling in mice. *Am. J. Resp. Crit. Care Med.* 177: 227-235, (2008).