

Mechanisms of Eukaryotic Gene Regulation by the Proteasome Complex In Vivo

Primary Investigator: Suresh R. Bhaumik
Funding agency: SIU Central Research Committee.

Gene regulation is fundamental to the proper functioning of a cell, and many human diseases can be traced to abnormal gene regulation. In eukaryotes, gene regulation is largely controlled at the level of transcription, which can be divided mechanistically into three different steps: initiation, elongation and termination. Several proteins and multiprotein complexes commonly known as “transcription factors” have been identified and characterized as regulating transcription both positively and negatively.

Proteasome, a so-called non-transcription factor, is essential for regulated protein degradation. It has recently been implicated in the regulation of transcription at the levels of initiation, elongation and termination. However, the precise mechanisms by which the proteasome regulates transcription in living eukaryotic cells remain largely unknown.

Evidence indicates the involvement of the proteasome complex in cancer and neurodegenerative diseases. Understanding the regulatory mechanisms of gene expression by proteasome components and their interactions with intracellular components will be crucial for designing better therapeutic approaches for these diseases

Using ChIP (Chromatin Immunoprecipitation) and FRET (Fluorescence Resonance Energy Transfer) methodologies, Dr. Bhaumik will determine *in vivo* mechanism of action of the proteasome complex in transcriptional initiation and elongation. In addition, he is developing a new application for FRET to identify the sub-unit interaction network of the proteasome complex in living eukaryotic cells.

Such a sub-unit interaction map will be useful for drug discovery efforts aimed at finding novel inhibitors of specific proteasome functions, since proteasome inhibitors have shown promising anti-cancer activity and their therapeutic index could conceivably be improved by a better topological and functional knowledge of this complex.

Role of Notch Signaling in Adipocyte Derived Stem Cells

Primary Investigator: Christopher Chambers, M.D.
Funding Agency: Plastic Surgery Education Foundation

Reconstructive surgery using engineered tissue constructs is a rapidly-growing therapeutic field. Adipose-derived adult stem cells (ADSCs) have been touted as an easily accessible, readily expandable, multi-potential cell population that could serve as one of the key components to a successful tissue engineering strategy. Adipose is tissue containing fat cells.

The aim of this project is to determine the effect of notch signaling on adipocyte derived adult stem cell proliferation and osteoblast differentiation potential. This project's hypothesis is that notch signaling regulates adult adipocyte derived stem cell fate decisions and restricts osteoblast differentiation of these cells.

ADSCs can be induced in culture to differentiate under specific culture conditions into adipogenic, osteogenic, chondrogenic, myogenic, endothelial and neural lineages. However, the mechanisms regulating the maintenance of this cell population *in vivo* is not known. While many investigators are interested in using this population in bone reconstruction procedures, the mechanisms regulating the osteogenic potential of ADSCs are similarly poorly defined. The Notch signaling pathway is an attractive target for regulating both stem cell maintenance in the adult and cell fate decisions of the uncommitted progenitors. Therefore, the goal of this study is to begin to make clear the role of Notch signaling on ADSCs *in vivo* and *in vitro*. Understanding how this cell population is regulated may allow the development of strategies that allow for increasing the expansion, osteogenic and *in vivo* recruitment potential of ADSCs to aid in tissue engineering and endogenous repair mechanisms.

Interferon-Gamma to Improve Macrophage Functions Against Mycobacterium Avium Complex Infection in HIV-Infected Patients

Primary Investigator: Janak Koirala, M.D.
Funding Agency: American Lung Association

Macrophages are special blood cells that engulf and destroy bacteria and foreign particles in the lungs and other organs. People with HIV infection experience a progressive decline in macrophage functions, which plays a significant role in their vulnerability to opportunistic infections, including a serious infection called Mycobacterium avium complex (MAC). MAC is an organism similar to the organism that causes tuberculosis. MAC causes lung and blood stream infection in patients with poor immunity. A defect in the means by which the body produces a substance called interferon-gamma (IFN-gamma) mediated by another substance called interleukin-12 (IL-12) has a significant impact on macrophage function in people with advanced HIV infection.

The goal of this research project is to make a comprehensive assessment of IFN-gamma production, to explore the mechanisms of its effect on cellular immunity, and to find ways to improve macrophage functions in HIV infected patients. This will help delineate more clearly the way HIV disease and opportunistic infections arise. Identifying individuals with a defect in IFN-gamma production and macrophage function will allow physicians to initiate appropriate measures earlier. Further exploration of measures to overcome such defects will be valuable in developing more effective treatment of mycobacterial infections in HIV-infected as well as non-HIV infected patients.

The research could lead to development of new treatments that will help patients more effectively fight lung infection. The ALA has funded Dr. Koirala's research for three years. His previous research focused on HIV and staph pneumonia.