Abstract:

The extracellular matrix, transmembrane receptors known as integrins, and associated signaling pathways are key components of cell adhesion and are thought to be a critical molecular system responsible for transducing information about the mechanical environment to the cell. The underlying idea for this postdoctoral research project is that beta 1 integrins play crucial roles in bone formation and in detection of mechanical stimuli. Recent transgenic animal studies from the Globus research group show that perturbing beta 1 integrin signaling in bone-forming osteoblasts causes skeletal abnormalities. Furthermore, results from the Almeida research group demonstrate that in cultured osteoblasts, beta 1 integrin transduces proliferative signals in response to increased gravity loading by centrifugation.

The postdoctoral research will test the hypothesis that beta 1 integrin is a required component of both bone formation and mechanosensing by developing novel in vivo and in vitro systems. The fellow will have the opportunity to generate an in vivo model for osteoblast-specific ablation of the beta 1 integrin gene in mice using established CRE recombinase-LoxP technology. Such a tissue-targeted approach to gene deletion is needed because conventional gene deletion results in embryonic lethality long before bone development begins. The mice lines needed to accomplish osteoblast-specific gene deletion are available in our laboratories. Analysis of the skeletal phenotype of progeny displaying osteoblast-specific ablation of beta 1 integrin will reveal the in vivo relevance of beta 1 integrin signaling for detecting skeletal loads generated by normal physical activity during growth and adulthood.

As a complimentary approach, the beta 1 integrin-null osteoblasts can be isolated to study integrin-dependent molecular events involved in detection of gravity and mechanical loading in vitro. To accomplish this, ground-based models of cell culture centrifugation and substrate deformation developed in our laboratories at Ames Research Center will be available to the fellow. Thus, this project will provide both novel information about the molecular functions of beta 1 integrin in mechanotransduction and gravity sensing, and the opportunity for a postdoctoral fellow to obtain training in complementary molecular approaches for analyzing the influence of gravity on living systems.

This project is co-sponsored by Dr. Globus and Dr. Eduardo Almeida because of their complementary expertise in animal physiology and cell biology.