

Bankhead-Coley Cancer Research Program

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Cancer Center
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Bridge (1-year project)

Project Title: The Role of PKR in a Novel IL-3 Signal Transduction Pathway

Project Summary: Recently the research team's laboratory has discovered a novel protein that regulates cell growth and protein synthesis by activating the dsRNA-dependent protein kinase, PKR. The team named this new protein PKR activator X, or RAX. The evidence indicates that a diverse range of cellular stresses, such as growth factor deprivation, treatment with inflammatory molecules or chemotherapy agents, and viral infection initiate RAX-dependent PKR activation to shut down protein synthesis and induce cell death. Furthermore, reduced levels of RAX protein promote inappropriate cell growth. Taken together, these findings suggest that RAX may be critical for preventing cancer, maintaining the correct composition of bone marrow cells, and initiating the response to infection from foreign agents. The team hypothesizes that RAX functions as a necessary direct upstream regulator of PKR in a Stress -> RAX -> PKR sequential signaling axis that regulates cell growth and promotes stress-induced cell death. However, the mechanism by which RAX activates PKR and regulates cell death is not yet clear. Therefore, the team identified the following specific aims:

1. To determine the molecular mechanism by which RAX activates PKR.
2. To determine the physiologic function of RAX in the context of a whole animal.

To achieve the first specific aim, the team developed RAX mutants and biochemical assays that will enable the identification of the regions of RAX that are required for proper function and what other proteins cooperate with RAX to promote the stress response. In addition, studies have been initiated that will reveal the three dimensional structure of the RAX protein in order to determine how RAX interacts with and activates PKR. As a tool to accomplish the second specific aim, "knockout" mice for the RAX gene will be generated that are identical to normal mice except for the single deficiency of the RAX gene and therefore the RAX protein. These mice will allow us to study the function of RAX in the whole animal and to determine the role for RAX in tumor formation and anti-viral defense. Using mice as a model organism allows for the study of many generations and large numbers of animals that have a similar blood system to humans in a relatively short amount of time and without having to use any human subjects. The results of these proposed studies will help to achieve the goals of the Bankhead-Coley Research Program by filling fundamental gaps in current understanding of the basic science of cancer and by fostering collaboration among cancer researchers at the University of Florida. In the future, increased knowledge of the mechanisms for RAX-dependent cell growth regulation may point the way to the development of new anticancer therapies.