NIH Award from the National Institute of Arthritis and Musculoskeletal and Skin Diseases

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- Project: Molecular Mechanisms of Cytoskeletal Rearrangement in Rheumatoid Arthritis
- Start Date: July 17, 2009
- Total Award Amount: $76,250

How the results of this project will benefit society:
Rheumatoid arthritis (RA) affects at least 1 percent of the population. Current therapies are only partially effective, and there is great need for more effective therapeutic approaches. We propose to identify novel molecular mechanisms that regulate the actin cytoskeletal rearrangement in synovial fibroblasts that contribute to the pathology of RA in order to define new therapeutic targets.

The problem the project is trying to solve:
An autoimmune disease, RA is associated with hyperproliferation and increased invasiveness of synovial fibroblasts (SFs), leading to joint damage. The mechanisms underlying SF cell transformation in RA remain poorly understood. However, it is expected that altered actin cytoskeletal remodeling contributes to their aggressive phenotype. Recently, we found that SFs isolated from RA patients (RASFs) express elevated levels of the actin cytoskeleton regulators actin filament associated protein of 110 kilodalton (AFAP1) and Abl tyrosine kinase compared to normal SFs and that they are able to form a complex. We propose that the interaction of AFAP1 and Abl contributes to the altered cytoskeletal rearrangement of RASFs and to the pathology of RA.

How this project will work:
In the first specific aim, we will examine the molecular properties of the Abl-AFAP1 complex and the molecular consequences resulting from the Abl-AFAP1 complex formation, particularly Abl activity and the ability of AFAP1 to bind and crosslink actin. Specific aim 2 utilizes knockdown and expression of an Abl binding mutant of AFAP1 to determine the functional effects of the AFAP1-Abl interaction in cell proliferation and migration/invasion of RASFs. It is important to understand the mechanism of the cytoskeletal rearrangement in RA in order to develop new treatment strategies that are designed to prevent joint destruction.

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