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CHARLES H. HOOD FOUNDATION ROLE OF SH3BP2 AS A NOVEL REGULATOR OF TNF-ALPHA PRODUCTION AND OSTEOCLASTOGENESIS.

Scientific Abstract

The goal of this proposal is to find the molecular mechanisms associated with SH3BP2 that are essential for tumor necrosis factor (TNF)-alpha production in macrophages and for osteoclastogenesis. We recently discovered that the signaling adapter protein, SH3BP2, is a previously unrecognized regulator of TNF-alpha generation in macrophages and of osteoclast differentiation. This progress in understanding the regulation of myeloid cell activation resulted from studies of the pediatric disorder, "cherubism".

Cherubism is a heritable and disfiguring craniofacial disorder characterized by the accumulation of inflammatory fibrous tissue with excessive bone degradation in the jaws. Using a genetic approach, we discovered several missense mutations in SH3BP2 in cherubism patients. To investigate how mutant SH3BP2 causes cherubism, we created a mouse model using the most common of these mutations. Homozygous cherubism mice exhibited systemic macrophage inflammation and M-CSF-induced high TNF-alpha production in macrophages. The result was severe inflammatory bone loss and joint destruction typically seen in patients suffering from rheumatoid arthritis. Bone marrow cells of both hetero- and homozygous mice showed increased sensitivity to RANKL and, therefore, enhanced osteoclastogenesis.

To explore the role of SH3BP2 in TNF-alpha production and osteoclast differentiation more precisely, we propose to characterize SH3BP2 interacting proteins in macrophages and osteoclasts using mass spectrometry. A second goal is to determine whether SH3BP2 plays a role in growth factor or cytokine production in osteoblasts. Such a detailed analysis of signaling complexes in which SH3BP2 participates will greatly contribute to better molecular understanding of inflammatory bone diseases. Importantly, the identification of the proteins that control TNF-alpha production would provide new targets for the development of more effective and safer drugs for the treatment of inflammatory bone diseases of children such as juvenile rheumatoid arthritis.

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Non-Technical Summary

Juvenile rheumatoid arthritis (JRA) and psoriatic arthritis are common diseases in childhood and frequently result in irreversible joint deformity and impaired function. It is estimated that 50,000 children suffer from JRA in the United States alone. In these conditions, tumor necrosis factor (TNF)-alpha, a soluble protein secreted from activated macrophages, plays a central role in causing joint inflammation and damage. TNF-alpha also enhances the development and activity of osteoclasts (bone resorbing cells) in the bones of affected joints, causing severe bone loss in arthritis. Although intensive research efforts have resulted in significant advances, much remains to be learned about which are the key molecules and cells that cause inflammatory arthritis.

Cherubism is an inherited and disfiguring inflammatory disorder of the jaw bones of children. A genetic approach to the study of this disease discovered mutations in SH3BP2, a protein involved in cell signaling, in cherubism patients and a mouse model was further created to investigate how mutant SH3BP2 results in cherubism. Using this model, it was recently discovered that SH3BP2 is a previously unrecognized key molecule for regulating TNF-alpha production in macrophages and osteoclast differentiation, both of which are important in producing inflammatory arthritis.

This project proposes to use this mouse model to identify other proteins that collaborate with SH3BP2 when it signals in macrophages and osteoclasts. Role of SH3BP2 in osteoblasts (bone producing cells) will also be explored. Detailed analyses of the molecular composition of signaling complexes in which SH3BP2 participates and of the mechanisms that control TNF-alpha production in macrophages and osteoclast differentiation should contribute greatly to a better understanding of the molecular mechanism of inflammatory joint disease and how bone is maintained. As a result, new targets would be available for the development of more effective and safer drugs for the treatment of rheumatic diseases of children.