Hypoxia and inflammation in Erdheim-Chester disease microenvironment: Insights on the pathogenesis and implications for therapy

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Abstract

Erdheim-Chester Disease (ECD) is a multi-system, non-Langerhans cell histiocytosis characterized by histiocyte infiltration of bones and often by extra-skeletal manifestations. When extra-skeletal involvement occurs, the prognosis is generally poor. The disease is extremely rare (about 350 published cases worldwide); however, the recent clustering of several ECD patients in our Institution (eleven patients diagnosed in a few years) suggests that its incidence is underestimated, and that a wider knowledge of its clinical presentation may help to diagnose unrecognized patients. The etio-pathogenesis of the disease is unknown. We have previously contributed to the understanding of ECD pathogenesis through the demonstration of a complex network of proinflammatory cytokines and chemokines at the lesion site, which might be responsible for the autocrine recruitment/retention and activation of ECD histiocytes.

In the present proposal, we aim to better define the pro-inflammatory microenvironment inside ECD lesions. Moreover we intend to evaluate the possibility to interfere with it by means of specific inhibitors already available for human usage, in order to find new therapeutic options for the disease.

ECD is a disease affecting otherwise healthy young and middle-aged individuals. When extraskeletal involvement occurs, the prognosis of the disease is severe. In such patients ECD causes a marked reduction in the life expectancy and usually leads to severe and invalidating complications (renal insufficiency leading to dialysis, heart failure, diabetes insipidus, pulmonary fibrosis, among others) requiring invasive and expensive treatments. No treatment has been shown effective so far in the long term control of the progression of the disease. Considering that ECD is an extremely rare disease, there is no interest from the pharmaceutical industry to support research for finding and testing new therapeutic strategies for this disease.

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With the exception of interferon (IFN)-α and imatinib, the therapeutic strategies for ECD have been substantially based on the use of antiblastic drugs or corticosteroids. The lack of a specific and pathogenetic treatment for ECD is undoubtedly due to the substantial lack of research on the pathogenesis of this disease.

The present study is expected to identify new molecular targets, that can be readily exploited for development of novel therapeutic strategies for ECD.