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New Frontiers in Innate Immune Memory

Title:
Role of Trained Immunity in the pathogenesis of Erdheim-Chester Disease

Authors:
Riccardo Biavasco [1], Marina Ferrarini [2], Elisabetta Ferrero [2], Eugenio Montini [1], Simone Cenci [3], Simone Cardaci [4], Angelo D'Alessandro [5], Davide Stefanoni [5], Lorenzo Dagna [6], Giulio Cavalli [6]

Affiliations:
[1] *Insertional Mutagenesis and Safety of Gene Therapy, Telethon Institute for Gene Therapy (SR-Tiget), San Raffaele Scientific Institute, 20132 Milan, Italy*
[2] *Experimental Oncology Unit, San Raffaele Scientific Institute, 20132 Milan, Italy*
[3] *Age related diseases Unit, San Raffaele Scientific Institute, 20132 Milan, Italy*
[4] *Cancer metabolism Unit, San Raffaele Scientific Institute, 20132 Milan, Italy*
[5] *Department of Biochemistry and Molecular Genetics, University of Colorado Denver, Aurora, CO 80045, USA.*
[6] *Unit of Immunology, Rheumatology, Allergy and Rare Diseases (UnIRAR), San Raffaele Scientific Institute, 20132 Milan, Italy*

Topic:
Innate immune memory

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Background:
Erdheim-Chester disease (ECD) is a chronic inflammatory disease characterized by infiltration of bone and other tissues by foamy macrophages. These cells exhibit activating mutations along the MAPK pathway, most commonly *BRAFV600E*, and increased production of pro-inflammatory cytokines. Although this dual neoplastic-inflammatory nature of ECD has long fascinated scientists, the mechanistic link between these two features remains elusive. We hypothesized that Trained Immunity (TI), a pro-inflammatory cell program physiologically elicited in monocytes/macrophages upon activation of the MAPK pathway, might represent the missing link between oncogenic transformation and pro-inflammatory activation in ECD.

Aim:
In this study, we aimed at determining the role of TI in the pathogenesis of ECD, and to evaluate the therapeutic potential of targeting this mechanism for the treatment of ECD.

Methods:

We developed innovative models to study ECD pathogenesis *in vitro* and *in vivo* (ectopic expression of BRAFV600E in monocytes), as well as *ex vivo* (3D culture of ECD tissues in bioreactor). Mechanistic features of TI, including typical changes in cell energy metabolism, were investigated by assessing I) cytokine and lactate production; II) mitochondrial respiration with Seahorse flux analyzer; III) glucose and glutamine metabolism with metabolomics analyses.

Results:
Activation of the MAPK pathway induced by BRAFV600E in ECD macrophages induces changes in the epigenetic landscape, cell energy metabolism, and cytokine production characteristic of TI. In particular, changes in cell energy metabolism of macrophages are characterized by increased glycolysis and glucose and glutamine metabolism. This metabolic rewiring is likely needed to sustain rampant, constitutive production of pro-inflammatory cytokines IL‑1β, IL-1α, and IL-6.

Discussion:
A role emerges for TI in the pathogenesis and pro-inflammatory activation of ECD. Since drugs targeting TI programs are already entering the clinical arena, the identification of this mechanism in the pathogenesis of ECD may translate into novel, effective treatment options for ECD patients.

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Word count of abstract body: maximal 350 words