A NOVEL AUTOINFLAMMATORY DISEASE CHARACTERIZED BY NEONATAL-ONSET CYTOPENIA WITH AUTOINFLAMMATION, RASH, AND HEMOPHAGOCYTOSIS (NOCARD) DUE TO ABERRANT CDC42 FUNCTION

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Objectives: to describe a novel hematological and autoinflammatory disorder in three unrelated patients caused by a de novo missense mutation of CDC42.

Methods: Whole exome sequencing was used to identify the novel variant. The functional impact of altered CDC42 function on hematopoiesis and inflammation was assessed through patient peripheral blood and bone marrow analyses, protein behavior and immune and non-immune cell functioning through in vitro biochemical and functional assays and in vivo C. elegans modeling.

Results: Patients shared the same de novo missense mutation of CDC42 (NM_001791, Chr1:22417990, c.556C>T, p.R186C). Disease features included neonatal-onset cytopenia with dyshematopoiesis, gout inflammation, rash, and hemophagocytosis (collectively termed NOCARDH syndrome) (Table). An altered hematopoietic compartment (prevalence of early differentiation elements and substantially decreased clonogenic progenitors) was demonstrated. Complementary assays documented the unique consequences of this mutation on CDC42 localization and function, and its disruptive effect on cell behavior and developmental processes, possibly linked to actin dysregulation. Increased secretion of IL-1β, and particularly of IL-18, was observed via ex vivo spontaneous release from unstimulated bone marrow mononuclear cells and by high levels in bone marrow supernatants and plasma. IFNγ was also increased and correlated to CXCL9 levels which were strictly related to ferritin levels. Treatment with anakinra and emapalumab, a monoclonal antibody to IFNγ, was identified as critical in the survival of one patient, who underwent successful hematopoietic stem cell transplantation.

Conclusion: The p.R186C amino acid substitution in CDC42 underlies a novel, unique syndrome where CDC42 functional dysregulation has pleiotropic effects, causing hematopoietic disturbance, hyperinflammation, and immune impairment. Early recognition and control of HLH, through neutralization of IFNγ, followed by hematopoietic stem cell transplantation, appear to be crucial to survival.

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FR0540 A NOVEL AUTOINFLAMMATORY DISEASE CHARACTERIZED BY IMMUNOCITOPENIA WITH AUTOINFLAMMATION, CHRONIC INTESTINAL DISEASE, AND HEMOPHAGOCYTOSIS


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REFERENCES:

Because of insufficient disease control, treatment with a TNF-inhibitor (infliximab) was started with apparent improvement of intestinal symptoms. However, persistent granulomatous inflammatory disease of the ileocecal region of the ileum as well as gastrointestinal ulceration occurred, which required supplementation with oral glucocorticoid. The ileus developed recurrences in spite of treatment with anakinra and emapalumab, a monoclonal antibody to IFNγ, was identified as critical in the survival of one patient, who underwent successful hematopoietic stem cell transplantation.

Conclusion: to describe a novel hematological and autoinflammatory disorder in three unrelated patients caused by a de novo missense mutation of CDC42.