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Ikaros family zinc finger 1 regulates dendritic cell development and function in humans

Cytlak U.[1], Resteu A.[1], Bogaert D.[2], Kuehn H. S.[3], Altmann T.[1], Gennery A.[4], Jackson G.[5], Kumanovics A.[6], Dullaers M.[2], Reichenbach J.[7], Hill H.[6], Haerynck F.[2], Rosenzweig S. D.[3], Collin M.[1], Bigley V.[1]
[1]Newcastle University, Human Dendritic Cell Lab, Institute of Cellular Medicine, Newcastle upon Tyne, United Kingdom
[2]Ghent University Hospital, Ghent, Belgium
[3]NIH Clinical Center, National Institutes of Health, Bethesda, MD, United States
[4]Newcastle University, Institute of Cellular Medicine, Newcastle upon Tyne, United Kingdom
[5]Newcastle University, Northern Institute for Cancer Research, Newcastle upon Tyne, United Kingdom
[6]University of Utah, Salt Lake City, UT, United States
[7]University Children's Hospital, Zurich, Switzerland

The prototypic functions of Dendritic cells (DCs) include the polarization of naïve T cells or induction of tolerance, but they also regulate a wide range of leukocyte responses. The diverse functions of DCs are represented by at least three subsets; conventional DC1 (cDC1), specialized in antigen cross-presentation, anti-tumor and vaccination responses; cDC2, the predominant IL-12 secretors in human; and IFN-a secreting plasmacytoid DC (pDC). The latter have been shown to support B cell proliferation, memory differentiation and immunoglobulin secretion and are implicated in the pathogenesis of multiple myeloma (MM).

Hematopoietic cell development and lineage specification is coordinated by transcription factors (TF), which may govern the expression of both differentiation and functional gene sets. Ikaros family zinc finger 1 (IKZF1) is a TF required for mammalian B cell development. IKZF1 deficiency also reduces pDC numbers in mice but its effects on human DC development are unknown.

Heterozygous *IKZF1* mutations in humans were recently identified as the cause of an immunodeficiency syndrome characterized by progressive loss of B cells, hypogammaglobulinaemia, T cell subset skewing, recurrent infections and autoimmunity. IKZF1 is also targeted for selective proteosomal degradation by the drug lenalidomide, used to treat multiple myeloma.

Enumeration, phenotypic and functional analyses were performed on peripheral blood monocyte and DC subsets in twenty affected individuals from four kindreds with heterozygous *IKZF1* mutations. Similar analyses were undertaken in cells with reduced IKZF1 protein levels resulting from in vivo or in vitro exposure to lenalidomide.

Loss of pDC, expansion of cDC1s and reduction in non-classical monocytes were consistent findings in patients with heterozygous IKZF1 mutations. pDC deficiency was replicated in myeloma patients and in vitro cultures treated with lenalidomide. DC functional assays revealed a reduction in IFN-a and IL-12 production in the context of genetic or pharmacological IKZF1 deficiency.

IKZF1 has an essential role in human DC development and function. The DC defects in IKZF1 deficiency may contribute to the immunodeficiency of IKZF1 haploinsufficiency but augment the therapeutic benefit of lenalidomide treatment in MM.