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STK4 (MST1) loss of function mutation: a cocktail of combined immune deficiency diseases

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Introduction

STK4 (serine Threonine kinase 4; formerly called MST1 is the mammalian homologue of *Drosophila Hippo*, the central constituent of a highly conserved pathway controlling growth and apoptosis. STK4 is a cytoplasmic protein that has pro-apoptotic and anti-apoptotic effect yet more linked to apoptotic machinery.[1,2]

STK4 stimulates FOXO1 expression an integral transcription factor essential for IL7R alpha expression on naïve T cells allowing their proliferation and survival - through down regulation of anti-apoptotic BCL2 expression, their egress from the thymus and their homing to secondary lymphoid organs-through down regulating homing receptors CCR7 and CD62L. (Figure 1).[3] STK4 deficient mice have progressive loss of T and B cells because of excessive apoptosis.[4,5] Up to date, 12 cases from 5 unrelated families (Iranian and Turkish origins) have been described to have STK4 deficiency,[6–8] Median age at clinical presentation was 2.5 years (range: Birth-10y). Recurrent superficial skin infections; bacterial, viral mainly Warts, *Molluscum Contagiosum* or fungal, Candidiasis together with susceptibility to Herpes *Simplex stomatitis* of variable degrees have been the most consistent clinical presentations among reported cases (Table 1). Moreover, some cases had evidence of autoimmune cytopenias and disseminated EBV viraemia with or without EBV related lymphoproliferation (LPD). Laboratory investigations revealed variable degrees of intermittent or persistent mild to severe neutropenia (not related to infections), CD4 lymphopenia, variable degrees of hypergammaglobinemia including raised IgE in some cases, raised transitional B cells and reduced non-class switched memory B together with presence of circulating auto-antibodies against variable antigens. Genetic analysis identified variable nonsense mutations in STK4 gene located on chromosome 20. STK4 deficiency has features that overlap with different primary immune defects (PID):

i. DOCK8 deficiency; eczema, molluscum and skin warts with raised IgE,
ii. ELANE defect cyclic or persistent neutropenia ,
iii. EVER1 and EVER2 epidermodysplasia verruciformis,
iv. PIDs with susceptibility to EBV LPD.

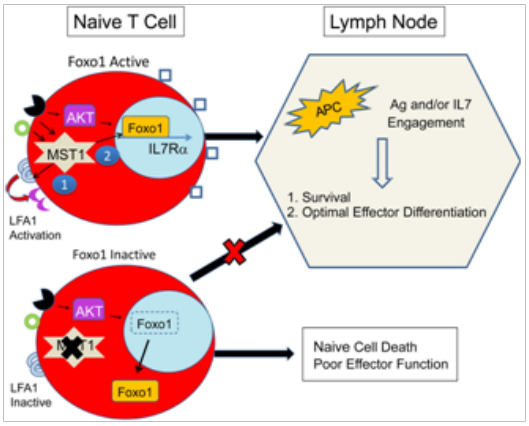

Figure 1 Proposed mechanism of immunodeficiency because of STK4 defect

Note: Proposed mechanism for immunodeficiency because of MST1 defects. MST1-deficient humans and mice exhibit significantly restricted populations of naive T cells. This is likely due to impairment of at least 2 primary roles of MST1, mediation of TCR (black receptor) and chemokine (green circle) driven integrin (LFA1) activation (purple crescent), necessary for T-cell adhesion and activation of Foxo1, necessary for IL-7Rα transcription.[1,2] In MST1 deficiency, unopposed AKT activity leads to phosphorylation and cytoplasmic shuttling of Foxo1 and impaired transcription of IL-7Rα, decreasing the sensitivity of naive T cells to IL-7. Naive T-cell survival is dependent on TCR and IL-7 exposure in the lymph node. In MST1 deficiency, lymph node entry is impaired because of poorly activated LFA1 (blue semicircles); IL-7R (blue squares) signalling is diminished; and T-cell stimulation by antigen-presenting cells (APCs) is suboptimal (also due to impaired LFA1 activation). Therefore, naive T cells die and effector cells undergo suboptimal activation and proliferation.
.Quoted from Risma.[3]

Table 1 Summary of clinical features of cases with STK4 defect

Presentation	Number and percentage
Superficial skin infections-bacterial	11/12; 91.6%
Superficial Skin infections-Viral (*Molluscum Contagiosum*, Warts, Varicella Zoster)	11/12; 91.6%
EBV viraemia	5/12; 41.6%
EBV LPD	2/12; 16.6%
EBV-driven lymphoma	1/12; 8.3%
Atopic or seborrheic dermatitis	6/12;50%
Upper and lower respiratory tract infections/bronchiectasis	8/12;66.6%
Autoimmune manifestations (AIHA, ITP, neutropenia; ANA+ve)	4/12;33.3%
Right sided cardiac anomalies;	4/12; 33.3%
PFO, ASD II, TI, PI	

Abbreviations: AIHA, autoimmune haemolytic anaemia; ITP, idiopathic thrombocytopenia; PFO, patent foramen ovale; ASD, atrial septal defect; TI, Tricuspid insufficiency; PI, Pulmonary insufficiency

Treatment includes antimicrobial, antifungal and antiviral prophylaxis. Hematopoietic stem cell transplant is the curative treatment for STK4 deficiency. To date, only 3 patients underwent a stem cell transplant for this disease; 2 of them passed away due to severe acute graft versus host disease.

Acknowledgments

None.

Conflicts of interest

The author declares that there is no conflicts of interest.

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