Abnormal Indian Hedgehog Signaling affects Distal Digit Patterning in a Mouse Model with Brachydactyly Type A1

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After graduating at the University of Melbourne with a major in Biochemistry with honours, Danny Chan started his scientific career in skeletal biology under the guidance of Professor Bill Cole at the Royal Children's Hospital, Melbourne. He continued with further postgraduate education at the University of Melbourne and obtained his Masters of Science in 1989 and PhD in Medicine in 1997.

Danny Chan maintained his research interest in skeletal biology and has contributed significantly to the molecular understanding of many forms of the human osteochondrodysplasias. In 1997, in recognition of his contribution, he was presented with an award for "Excellence in Medical Research" by the State Premier of Victoria, Australia. He joined the Department of Biochemistry at The University of Hong Kong in 1999, where his research contributed to the success of the Area of Excellence Programme in "Developmental Genomics and Skeletal Research" in 2004.

Brachydactyly type A1 (BDA1) is the first recorded disorder of the autosomal dominant Mendelian trait. It is characterized by mild dwarfism and pronounced shortening or absence of the middle phalanges. Recently, the Indian hedgehog (*IHH*) gene has been shown to be associated with this disorder, with heterozygous missense mutations identified in the active N-terminal domain. *IHH* is expressed by prehypertrophic chondrocytes in the growth plates of long bones that regulates the tightly coordinated programme of chondrocyte proliferation and differentiation, a key process in endochondral bone formation. Its association to BDA1 suggests a role in distal digit patterning; particularly, in the formation of the ultimate phalangeal joint. The formation of this joint is interesting as it is influenced by signals from a number of surrounding tissues including FGF signals from the apical ectodermal ridge, BMP signals from the inter-digital regions, and Wnt14 and Gdf5 signals from within the interzone region (site of the future joint) of the cartilage anlagen.

To understand the molecular basis of the digit abnormalities in BDA1, a mouse model carrying an amino acid substitution (E95K) mutation in the mouse *Ihh* gene was generated by gene targeting. Homozygous mouse mutants ($Ihh^{E95K/E95K}$) showed distinct characteristics of the BDA1 phenotype with severe shortening or absence of the middle phalanges. Heterozygous mutants ($Ihh^{E95K/+}$) showed a mild phenotype with shortening of middle phalange of the fifth digit only. Compared to wild-type mice, *Col10a1* expression in long bones revealed mild to severe delayed endochondral ossification in $Ihh^{E95K/+}$ and $Ihh^{E95K/E95K}$ mice, respectively. At the early stages of digit formation (E13.5-15.5), *in situ* hybridization showed IHH signalling is down-regulated in $Ihh^{E95K/E95K}$ mice, with reduced expression of target genes (*Ptc and Gli1*) at the normal sites, but are abnormally activated in the periarticular region, indicating an altered signalling range. In addition, joint formation is delayed in $Ihh^{E95K/E95K}$ mice demonstrated by the late onset expression of *Wnt14* at the interzone. This study has provided the first insight into the molecular changes in BDA1 and the involvement of hedgehog signalling in the formation of distal digit joints.

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regulated IL-1RI and TLR4 but not TLR3 signaling by sequestrating the adaptors MyD88 and Mal. Macrophages from the $ST2^{-/-}$ mice produced significantly less IL-6, IL-12 and TNFα compared to cells from the wild-type mice when stimulated *in vitro* with IL-1 or LPS. In contrast to wild-type mice, ST2 deficient mice failed to develop endotoxin tolerance. Thus, ST2 suppresses IL-1R and TLR4 signaling via the MyD88- and Mal-dependent pathways and modulates innate immunity. These findings provide a molecular explanation for the role of ST2 in Th2 responses since inhibition of TLRs will promote a Th2 response and also identify ST2 as a key regulator of endotoxin tolerance.

This report illustrates the intricate balance between host defense against pathogens and avoidance of autoimmune disease.