ASBMR 2013 Annual Meeting

Loss of the E3 Ubiquitin Ligase Von Hippel Lindau (VHL) in Limb Bud Mesenchyme causes dwarfism and tumors of the soft tissue

Category: Bone, Cartilage and Connective Tissue Matrix & Development

Plenary Sessions, Presentation Number: FR0109
Session: Welcome Reception & Plenary Poster Session
Friday, October 4, 2013 5:45 PM - 7:00 PM, Baltimore Convention Center, Discovery Hall-Hall C

Poster Sessions, Presentation Number: SA0109
Session: Poster Session I & Poster Tours
Saturday, October 5, 2013 12:00 PM - 2:00 PM, Baltimore Convention Center, Discovery Hall-Hall C

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Adaptation to low oxygen tension is a critical event in fetal development. The hypoxia inducible factor-1 (HIF-1) and HIF-2 are essential mediators of the homeostatic responses that allow hypoxic cells to survive and differentiate. Our working hypothesis is that gradients of oxygen control organ size and shape during development by regulating the HIF signaling pathway. Along these lines, we have demonstrated that HIF-1 is an indispensable survival and differentiation factor for fetal chondrocytes, whereas HIF-2 is not necessary for fetal growth plate development. VHL is the E3 ubiquitin ligase that targets HIFs to the proteasome for degradation in normoxia, and it is also a tumor suppressor gene. In this study we analyzed the role of VHL in the context of endochondral bone formation.

We conditionally deleted VHL in whole limb bud mesenchyme by using the Cre-loxP system. Mutant mice were born with the expected mendelian frequency, but they died three-four weeks later. Prenatally, mutant cartilaginous elements lacking VHL were short and misshapen. This phenotype was due, at least in part, to a delayed transition from proliferation to hypertrophy, and from hypertrophy to bone marrow cavity formation. Moreover, chondrocyte proliferation rate was impaired.

Postnatally, VHL deficient chondrocytes underwent massive cell death that eventually caused to the collapse of the growth plate, and was paradoxically associated to a dramatic increase of trabecular bone, expansion of the bone marrow stroma and dilated bone marrow blood vessels.

In addition, VHL deficiency caused massive fibrosis in the synovial space associated to partial destruction of articular surface cartilage. More strikingly, in about 70% of the analyzed mice, loss of VHL led to the formation of fibroblastic tumors of the soft tissue, which aggressively invaded and destroyed the surrounding cartilaginous, muscular and bony structures.

In double mutant mice lacking both VHL and HIF-2 in limb bud mesenchyme, synovial fibrosis was partially corrected; though fibroblastic tumors were still detectable in at least 46% of the cases. Conversely in VHL/HIF-1 double mutants, these tumors were no longer present.

Taken together, our findings demonstrate that loss of VHL in mesenchymal cells controls size and shape of the skeletal elements, and its loss causes HIF-1 dependent aggressive fibroblastic tumors of the soft tissue.

Disclosures: None

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