Analyses of gene knockout mice for aggrecan and link protein: The roles of extracellular matrix in skeletogenesis

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Cartilage provides the template for endochondral ossification and is crucial for determining the length and width of the skeleton. During endochondral bone formation, hypertrophic chondrocytes die and cartilage is replaced with bone matrix. Proteoglycan aggregates of aggrecan, hyaluronan and link protein provide cartilage with tensile strength and elasticity. Here, we describe abnormalities of skeletal development in gene knockout mice for aggrecan and link protein (LP). Cartilage matrix deficiency (cmd) mice are a spontaneous knockout model of aggrecan, characterized by dwarfism, and die shortly after birth. The heterozygous cmd mice are born normal, but develop slight dwarfism and die earlier than the wild type by sudden onset of gait disturbance due to spinal misalignment. The LP knockout homozygotes show defects in cartilage development and delayed bone formation with short limbs and craniofacial anomalies. Most LP-null mice died shortly after birth due to respiratory failure but some survived and developed progressive dwarfism and lordosis of the cervical spine. The cartilage contained significantly reduced aggrecan deposition in the hypertrophic zone, and decreased numbers of prehypertrophic and hypertrophic chondrocytes. Reduced Indian hedgehog (Ihh) expression was observed in prehypertrophic chondrocytes, and apoptosis of hypertrophic chondrocytes was inhibited. These results indicate that LP is important for the formation of proteoglycan aggregates and normal organization of hypertrophic chondrocytes, and suggest that cartilage matrix plays a crucial role in chondrocyte differentiation and maturation.