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Role of autophagy in chondrocyte differentiation

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Maintaining cell homeostasis during cellular differentiation is critical for the cell survival. Therefore, the balance between protein biogenesis and degradation is tightly regulated. The removal of the after-used and unwanted substances is not only important for protein turnover but also in regulating cellular differentiation and developmental process. The degradation of protein relies on two well-known systems, the Ubiquitin-proteasome system (UPS) and Autophagy-lysosomal system (ALS). Here, using the unique organization of the growth plate that depicts temporal and spatial "life time" of chondrocytes during their differentiation process, we investigate the role of protein degradation systems during endochondral ossification. Both degradation systems are active during normal chondrocytes differentiation with different level of activity. Interestingly, ALS, in contrast to UPS, it is dynamically regulated in normal growth function. While ALS-related genes are expressed in all zones of the growth plate, autophagy activity is differentially activated during the differentiation process, being high in proliferating chondrocytes, lowest in hypertrophic chondrocytes, but increases again at the cartilage-bone junctions.

Using a mouse model (13del) for metaphyseal chondrodysplasia type Schmid (MCDS), ALS was further studied to better understand its roles in chondrocytes differentiation under pathological condition. In addition, in 13del mouse (MCDS mouse), autophagy is also found to participate in allowing stressed hypertrophic chondrocytes (HCs) to undergo "cell reprogramming" process, which was observed as a mechanism for HCs to alleviate ER-stress caused by the expression of unfolded mutant type X collagen protein. The full clearance of the abnormal protein is allowing stressed HCs to "complete" reprogram to less differentiated status. To address the role of autophagy in this context, we modulated autophagy activation using Rapamycin administration or by genetic inactivation of p53. Rapamycin enhances autophagy by inhibiting mTOR pathway while p53, which is up regulated in stressed HCs, is also known to regulate autophagy. Rapamycin treatment showed only mild activation of autophagy with no observable differences in HCs differentiation at p10. Inactivation of p53 in 13del mice indicated an effect on chondrocyte differentiation, but changes in autophagy were not observed. In conclusions, our descriptive analysis showed an association of autophagy to chondrocyte differentiation process, but mechanistic insights require more specific perturbation of autophagy pathway with additional drugs and genetic studies such as inactivation of Atg5 at specific differentiation stages of chondrocytes in both wild type and 13del mice.