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A trip to the world of endoplasmic reticulum stress

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Various pathophysiological conditions, such as calcium depletion, oxidative stress, hypoglycemia, expression of mutated proteins and hypoxia, interfere with the correct folding of proteins and these misfolded or unfolded proteins accumulate in the endoplasmic reticulum (ER). These conditions, which are collectively termed ER stress, have the potential to induce cellular damages. The ER responds to these perturbations by activating an integrated signal transduction pathway, called the unfolded protein response (UPR). Activation of the UPR leads to a transient translational attenuation to decrease the demands made on the organelle, transcriptional induction of genes encoding ER-resident chaperones to facilitate protein folding, and ER-associated degradation (ERAD) to degrade the unfolded proteins that have accumulated in the ER. In mammalian cells, ER stress sensing and signaling involves three well-established and ubiquitous ER stress transducers: PKR-like endoplasmic reticulum kinase (PERK), inositol-requiring enzyme-1 (IRE1) and activating transcription factor 6 (ATF6). Recent studies have implicated the failure of the UPR in various diseases such as neurodegenerative disorders, diabetes, skeletal diseases, etc. To develop therapeutic strategies for these diseases, further insight into ER stress and its stress response is needed. In this lecture, I would like to introduce the molecular mechanisms and the physiological functions of the UPR system, and the relationship between the perturbation of ER functions and pathophysiology of some diseases.

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Molecular mechanisms regulating tendon and ligament formation

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Ligaments bind bones together to stabilize joints, while tendons connect muscles to the skeletal elements and function as mechanical force transmitters. Cells in tendons and ligaments are specialized fibroblasts known as tenocytes and ligamentocytes, respectively. In the early stages of musculoskeletal development, progenitor cell populations for the musculoskeletal components migrate and settle down in the prospective region to give rise to cartilage, muscle, tendon, and ligament primordium. Each primordium for the musculoskeletal component initially develops as an individual unit, but subsequently tendons and ligaments integrate each musculoskeletal component into a single functional unit by a previously unknown mechanism. During postnatal growth, hyaline cartilage in the chondrotendinous/chondroligamentous junction (CTJ/CLJ) is gradually replaced by bone and fibrocartilage to generate the fibrocartilaginous enthesis in the osteotendinous/osteoligamentous junction (OTJ/OLJ). *Sox9*, a SRY-related transcription factor containing a high-mobility-group box DNA-binding domain, is an important regulator for cartilage formation. In the tendon/igament cell lineage, *Scleraxis* (*Scx*), a basic helix-loop-helix transcription factor, is persistently expressed throughout differentiation. Scx positively regulates the expression of *Tenomodulin* (*Tnmd*), a type II transmembrane glycoprotein predominantly expressed on mature tenocytes and ligamentocytes. Our lineage tracing studies indicate that the *Scx*$^{+}$/*Sox9*$^{+}$ progenitor population is a unique multipotent cell population that gives rise to tenocytes, ligamentocytes, and chondrocytes. In this lecture, I would like to talk about how the junction between the skeletal element and tendon/ligament (CTJ/CLJ and OTJ/OLJ) is established by the Scx^{+}/Sox9^{+} cell population.