Abstracts

S3-2
Induction of aggrecanases in cartilage by fibronectin fragments is mediated by α5β1 integrin and TLR4.

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Abundant extracellular matrix (ECM) components in cartilage are important in maintaining the joint function and the degradation of the ECM is the main cause of osteoarthritis (OA). This process progresses upon ageing accompanied by an increased production of matrix-degrading metalloproteinases. While tissue injury, mechanical loading, inflammatory cytokines and growth factors are considered to stimulate cartilage catabolism, endogenous factors that sustain the prolonged production of destructive proteinases in adult cartilage have not been clearly defined. A series of recent studies demonstrating that ECM components, when degraded by proteinases, reveal cryptic biological functions including induction of matrix metalloproteinases (MMPs) led us to consider the role of fibronectin fragments (FNfs) in cartilage degradation, because the synthesis of FN is elevated and its fragments are found in OA cartilage. We identified two key regions in FN located in type III repeats, III (8-10) and III (14), which induced cartilage aggrecan degradation. The degradation of aggrecan was primarily due to the elevated activity of aggrecanases. The fragment III (8-10) contains two integrin binding sites and the III (14) has an integrin binding site and a heparin binding site. The action of III (8-10) region is mediated through α5β1 integrins and that of III (14) through TLR4. Fragments III (8-10) and III (14) acted synergistically with each other and with IL-1 or TNFα. These studies suggest the complexity of inductive stimuli that cause cartilage matrix catabolism.

S3-3
Studies from TACE Mutant Mice

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The TNFα converting enzyme (TACE/ADAM17) is involved in the proteolytic release of the ectodomain of diverse cell surface proteins with critical roles in development, immunity and hematopoiesis. As the perinatal lethality of TACE-deficient mice has prevented an analysis of the roles of TACE in adult animals, I took advantage of the Cre-LoxP system and generated conditional Tace-deficient mice. Using this mutant line, I previously showed that TACE- inactivation in myeloid cells or temporal inactivation offers strong protection from endotoxin shock lethality in mice by preventing increased TNFα serum levels [1]. To gain further insight on the roles of TACE in vivo, I next generated a mutant line in which a Cre recombinase gene is expressed under the control of a Sox9 promoter [2]. SOX9 is an essential transcription factor for skeletal development and is expressed in all osteo-chondroprogenitor cells as well as in many other organs, including the pancreas, heart, lung, brain and skin, but not in hematopoietic cells. These mutant mice survived up to 9-10 months, but exhibited severe growth retardation as well as skin defects and infertility. The analysis of the skeletal system revealed shorter long bones and prominent bone loss, characterized by an increase in osteoclast and osteoblast activity. In addition, these mice exhibited hypercellularity in the bone marrow and extramedullary hematopoiesis in the spleen and liver. Flow cytometric analysis of the bone marrow cells showed a sharp increase in granulopoiesis and in the population of c-Kit+ Sca-1 lineage- cells, and a decrease in lymphopoiesis. Taken together, these observations reveal unexpected involvements of TACE in normal growth, skin development, bone metabolism and hematopoiesis, and therefore further underscore the importance of ectodomain shedding in vivo.