Matrix Effect on Chondrogenesis: Implication on Cartilage Repair
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Several million people suffer from joint cartilage damage with very debilitating conditions. Once damaged, cartilage is a tissue that does not restore itself. Techniques such as micro-fracture, autogenous or allogeneous osteochondral transplantation, and autologous chondrocyte implantation may be done to repair cartilage and relieve the patients’ symptoms. The environmental factors’ effect on the chondrogenesis, such as artificial matrix (scaffold) or natural derived matrix, will be discussed in this lecture.

Matrix effect on ACI: Autologous chondrocyte implantation (ACI) is US FDA proved technique for articular cartilage repair. It is a three – stages procedure including cartilage harvesting, chondrocyte expansion and cultured chondrocytes implantation. In the first generation of ACI, the periosteal flap is applied on the defect site to avoid cell leakage. However, periosteum hypertrophy or delamination is frequently seen complications. In the advanced ACI, artificial matrix membranes are used to replace periosteum, such as collagen I/III membrane (MACI). This technique significantly reduced the complication of periosteal hypertrophy. Another advanced ACI techniques, a chondrocytes were cultured in 3D matrices such as Hyaluronan based scaffold, type I collagen, fibrin/HA hydrogel, agarose/alginate scaffold (Hyalograft C, CaReS, NeoCart, BioCart II, Cartipatch). They can interdigitate with the defect sites well, reduce the releasing rate of chondrocytes and the cells have fewer tendencies to de-differentiate due to the three dimensional culture conditions.

Matrix effect on microfracture: In order to introducing mesenchymal stem cells (MSCs) from the subchondral blood vessels for cartilage tissue repair, the marrow stimulating procedure such as micro-fracture has become a first-line arthroscopic treatment method for small, symptomatic chondral lesions. After microfracture, the fibrin clot is filled the cartilage defect and covered the exposed bony surface. In order to producing a more hyaline-like repair capable of cartilage, augmentation of the microfracture procedure with scaffold is used in recent study. Different types of collagen, hyaluronic acid, Chitosan and growth factors were used for microfracture augmentation (BST-CarGel, MaioRegen, Chondro-Gide). Bi-phasic scaffolds (CRD, TRUFIT) also were used for osteochondral repair from endogenous MSCs from the
defect. Results showed the quality of the repair tissue is improved and offer exciting potential options for clinical application.

**Matrix effect on MSC chondrogenesis:** Due to the necessity of cartilage biopsy surgical procedure for ACI, some researchers had used MSCs as cell source for cartilage repair. Our previous study showed TGF-beta induced MSCs in type I collagen gel resulted in better chondrogenesis than pellet culture. Our preclinical animal study and clinical trial had also been performed. Many clinical trial studies had also used type I collagen as scaffold for MSCs cartilage repair. However, type X collagen expression is frequently seen. Our research about cartilage fragment from human osteoarthritis (OA) knee has been wrapped into fibrin glue with MSC and implanted on the back of nude mice. Results showed that the gene expression of type II collagen and type X collagen expression is reduced. When considering commercialization for clinical practice, the DNA remnants must be removed to reduce the side effect. Therefore, we try to fabricate human or porcine acellular cartilage matrix (ACM). Results showed human OA ACM powders had the potential of promoting type II collagen gene expression in the growth factors-absent environment. Moreover, different decellularization process of porcine cartilage has also been evaluated. Either cartilage fragment or ACM can reduce the type X collagen expression in MSC chondrogenesis.

**Future Perspectives:** Recently, many researchers are actively evaluating and developing new generation scaffolds or hydrogels for effective and reliable autologous chondrocyte implantation techniques and augmentation of microfracture. Based on the knowledge of matrix effect on chondrogenesis, combining ECM-mimic scaffold and autologous chondrocyte implantation techniques, microfracture and MSCs should be a promising treatment in the future.