Biological therapy and tissue engineering approaches for the treatment of osteoarthritis

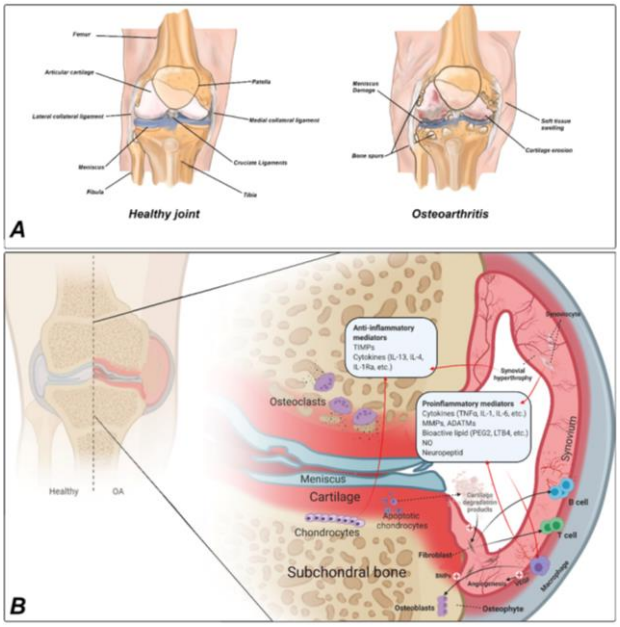

Figure 1.(A) Schematic representation of a healthy and osteoarthritic knee joint. (B) Biochemical environment of an osteoarthritic joint showing the pro- and anti-inflammatory mediators involved in OA (Picture: R. Ziadlou).

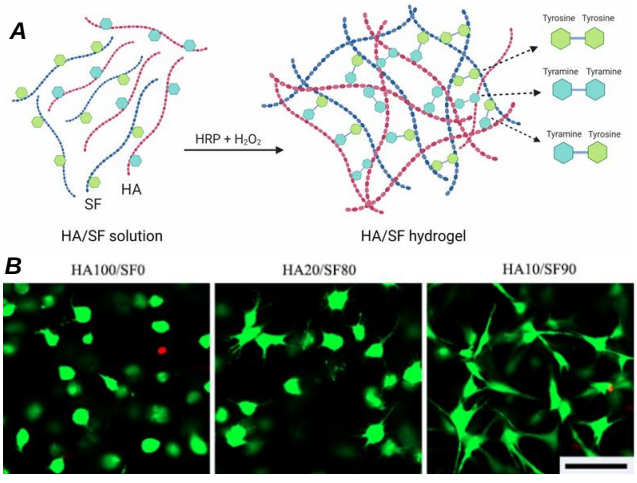

Figure 2.(A) Schematic illustration representing the potential covalent crosslinking in HA-SF composite hydrogels which can occur between tyramine residues of HA and tyrosine in the silk after enzymatic crosslinking. (B) Cell viability for the cell-laden hydrogels with live-dead assay representing the morphology of the cells in the hydrogels at day 7 of culture in chondrogenic medium. Scale bar: 100 µm (Picture: R. Ziadlou).

PhD-Thesis by Reihane Ziadlou.

In this thesis, we aimed to find an effective biological therapy to treat or impede osteoarthritis (OA) and to regenerate damaged articular cartilage. To achieve this goal, inhibition of pro-inflammatory cytokines that are excessively abundant in OA joints is necessary (Figure 1). Furthermore, for regeneration of damaged cartilage, it is essential to increase the chondrocytes anabolism for cartilage tissue to recover. Pharmacological therapy and tissue engineering approaches are the two most promising strategies towards cartilage regeneration.

Currently, there is no effective pharmacotherapy featuring both anti-inflammatory and anabolic effects to restore the degenerated cartilage in OA or other degenerative joint diseases. Therefore, we used an inflammatory model of human OA chondrocytes microtissues, in which after screening of 34 herbal compounds with potential anti-inflammatory and anabolic effects, VA, Epi C, PS, PCA, 4-HBA and 5-HMF were selected for further studies (1). We selectively identified the mechanism of action of Vanilic acid (VA) and Epimedin C (Epi C). Our results indicated that VA had significant anti-inflammatory effects through inhibition of IKK complex in NF-κB signaling and Epi C showed a significant anabolic effect by increasing the expression of collagenous and non-collagenous matrix proteins (2). Additionally, we developed a tunable and injectable hydrogel for drug delivery and cartilage tissue engineering by crosslinking different concentrations of HA-Tyramine (HA) with aqueous Silk-fibroin (SF) solutions (3). HA20/SF80 composite hydrogel showed the longest and the most sustained release profile for VA and Epi C over time, which is necessary for the long treatment duration for OA joints. Also, we showed superior ECM production in HA20/SF80 chondrocyte-laden constructs (Figure 2). For future studies, to achieve a successful therapy, the combination of all mentioned approaches in an *ex vivo* cartilage organ culture model and in animal models is envisioned.

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(3)) Ziadlou R, et al. Optimization of hyaluronic acid-tyramine/silk-fibroin composite hydrogels for cartilage tissue engineering and delivery of anti-inflammatory and anabolic drugs. Materials Science and Engineering: C 2020