Host Response to Biomaterial Scaffolds Implanted into Osteochondral Defects in Rabbit Knees with Rheumatoid Arthritis

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Introduction: Tissue engineering (TE) offers the promise of restoring arthritis diseased or damaged cartilage or bone and renewing joint function. Effective application of TE solutions for RA will require consideration of the construct in the associated intense inflammatory and immune environment. TE constructs in the RA environment must evade the disease process and the natural host defense system to avoid rejection by the immune system and/or the consequences of inflammation. The objective of this research was to assess the influence of the RA situation on the host response to orthopedic biomaterials and to identify biomaterials which would be useful for tissue engineering in the RA situation as a basis on which to develop a TE strategy. Often, the host response to biomaterials is assessed in healthy animals however the actual clinical application of the medical devices is typically in diseased patients. This research aims to address this gap. The animal model presented here involves the novel combination of a biomaterial implantation into an osteochondral defect of the femoral condyle of a rabbit with existing induced RA. A rabbit antigen-induced arthritis (AIA) model was used to induce RA. Of immune cells involved in RA, dendritic cells (DCs) have been shown to play a central role not only in the initiation and perpetuation of RA. The phenotype of DCs has also been shown to be modulated by biomaterials used in TE wherein poly(lactic-co-glycolic acid) (PLGA) scaffolds (SCs) induced DC maturation while agarose SCs did not[1].

Methods: AIA RA was induced in male New Zealand white rabbits (3 kg) by immunization on day 0 with subcutaneous (SubQ) injection of ovalbumin (OVA) emulsified in Freund's Complete Adjuvant (CFA)[2]. On day 14, rabbits were boosted by SubQ injection of OVA and Freund's incomplete adjuvant (IFA), followed by arthritis induction by intra-articular injection of OVA/PBS into the right knee joint per rabbit on day 21. One day later (day 22), PLGA or agarose SCs were implanted into the osteochondral defect formed in the right knee joint[3] (the left knee remained untreated as a within-animal control). On days 21, 22, 25, 29, and 36 (endpoint), joint swelling was measured to assess RA state, joint lavages and peripheral blood samples were collected to assess total leukocyte concentrations or differential leukocyte profiles. Histology and micro CT assessments of joints at the endpoint were performed and presented in a companion abstract.

Results: Upon RA induction and biomaterial implantation, the knee swelling size and total leukocyte concentration of the right knee joints significantly increased, compared to the untreated left knees. Induction of RA (with or without SC implantation) shifted to profile of leukocytes to in joint lavages to predominately granulocytes

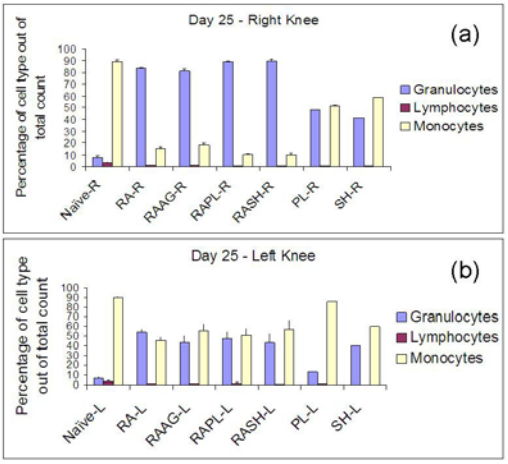

Figure 1. Differential leukocyte profiles in the joint lavage were observed at differential levels depending on biomaterial implantation and/or RA induction in the right knee joint (a). The profiles in the untreated left knee joints are also shown (b). Data for the Day 25 time point, 3 days after biomaterial implantation is shown. Abbreviations: RA – RA induction into the right knee joint, AG - agarose SC implantation into the right knee, PL – PLGA SC implantation into the right knee, SH – sham operation into the right knee. R – right knee, L – left knee.

(eosinophils and neutrophils) with a most significant effect in the right knee (Fig.1). Naïve rabbits showed a leukocyte profile in joint lavages which was primarily monocytes. Rabbits with knees undergoing sham operations or implantation of PLGA SCs (either without induced RA) showed a more balanced proportion of granulocytes and monocytes, which by 36 days resolved to a naïve rabbit profile. Agarose implantation into the RA knee joint induced joint swelling ratio significantly lower than sham operation in the RA knee joint on Day 29, whereas PLGA implantation into the RA knee joint induced significantly higher levels of total leukocyte concentration in the right (on Day 25 and 29), left knee (all time points) joint, or in peripheral blood (on Day 29), compared to controls or other treatments.

Discussion and Conclusions: Differential levels of host responses to biomaterials were observed when they were implanted into the knee joint of RA-induced rabbits consistent with *in vitro* studies of differential effects of biomaterials on DC phenotype

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