A SCID-HU CHIMERA MODEL WITH PERIPHERAL BLOOD MONOCYTES TRANSFUSION FOR OSTEOLYTIC PROSTHESIS FAILURE

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Introduction: The exact pathogenesis of aseptic loosening following total joint replacement remains not clear; although evidence indicates wear debris generated at interface between the implant component and surrounding bone play a critical role in the formation of periprosthetic tissue and osteolysis. We hypothesize that the circulating peripheral blood monocytes respond to the stimulation of wear debris generated at the prosthetic site and contribute to formation of the periprosthetic tissue and in turn lead to local bone resorption. This study describes a novel mouse model combining human periprosthetic tissue and bone chips, with transusion of autologous peripheral blood mononuclear cells to study the interactions that lead to wear debris-associated loosening. The host SCID (severe combined immunodeficiency) mice do not reject human xenografts, due to the lack of functional T and B lymphocytes.

Materials and Methods: Human periprosthetic tissues and bone chips were obtained from 5 OA patients with aseptic prosthetic joint loosening at the time of revision surgery. Tissue was diced into uniform pieces of 1x1x1 mm3 and bone pieces trimmed as 1x2x2 mm. One piece of bone was mixed with 2 to 3 periprosthetic tissue dices to implant into left quadriceps and paravertebral muscles of SCID mouse. Human peripheral blood monocytes (PBMC) from the same patient donor were isolated and purified. Cells were then labeled with PKH2 green fluorescent dye and cultured for three days before intraperitoneal injection into each operated mouse at 5 million PBMCs per mouse. To study whether the host residual dye and cultured for three days before intraperitoneal injection into each operated mouse at 5 million PBMCs per mouse. To study whether the host residual immune cells is necessary in the establishment of the periprosthetic tissue and local bone resorption.

Results: The human prosthetic tissues and implanted bone chips were well accepted in SCID mice. The viability and general morphology of the periprosthetic tissues was consistent between the engrafted tissue and the original tissue before implantation. However, multinucleated osteoclast-like cells were dramatically increased at the bone surfaces within the periprosthetic tissue, and focal bone erosions were ubiquitous. Cell densities within the implanted human tissue were significantly increased (Figure 1, p<0.05) following PBMCs transfusion. The fluorescent signals from labeled human PBMC remained at least 5 weeks in vitro. To trace in vivo cell trafficking, frozen sections of human tissue xenografts and host liver, spleen, lung tissues were examined under a fluorescent microscope. Extensive fluorescent cells were detected in periprosthetic tissue xenograft (Figure 2), although scattered human cells were also readily traced in spleen. There were no fluorescent cells detected in other tissues. Immunohistochemical staining for human CD68, CD14 and RANKL identified strong positive cells in the implanted human tissues. It is also noticeable that mouse-origin macrophages (mouse CD68 positive cells) were presented in the xenografts, especially at the interface areas of host-engrafts. Total cell numbers in tissues with ASGM1 antibody treatment were apparently less than that in PBS-control group, indicating the successful depletion of the host immune cells (Figure 1). mRNA expression of RANK, cathepsin K (CPK), calcitonin receptor (CTR), IL-1, IL-6 and TNF in xenografts were comparable with the periprosthetic tissue before implantation. ELISA for human IL-1 and IL-6 levels in xenograft homogenates showed elevated expression in PBS group than the ones with the ASGM1 group. MicroCT evaluation suggested the trend of BMD decreases of the bone implants.

Discussion: This study extends our previously investigation on the SCID-human mouse model of aseptic looseness, as including trabecular bone along with periprosthetic tissue in the SCID mouse hosts. Transfused PBMC were attracted to the periprosthetic tissue implantation sites. However, it appeared that the host residual murine immune cells also participate in some level of cell composition of the implanted tissue at end of the experiment. Pretreatment of ASGM1 antibody to deplete the host residual immune cells is necessary in the establishment of the SCID-human mouse model. Further study has been carrying on investigating the properties of wear debris in activation of PBMC to participate the formation of the periprosthetic tissue and local bone resorption.

Figure 1: cell counts in xenografts 14 days after implantation. ASGM1 and PBS groups were with PBMC transfusion, and control group went through human tissue engraft without PBMC introduction.

Figure 2: PHK2-labeled PBMC in xenograft at 14 days after implantation (100x).