Temporal Alterations in Gene Expression of Swarm Rat Chondrosarcoma Transplanted into Bone

Bell, JE; Gomez, P; Stevens, J; Sabesan, V; Kurriger, G; Soares, B; Morcuende, JA
University of Iowa Hospitals and Clinics, Iowa City, IA
john-erik-bell@uiowa.edu

Background: Chondrosarcoma is the most common primary malignancy of bone in adults. It grows slowly, eventually destroying local host bone and metastasizes late, usually to the lungs. Little is known about the molecular changes that occur as this often fatal progression occurs. The Swarm rat chondrosarcoma (SRC) is a naturally occurring tumor that histologically and radiographically resembles Grade II human chondrosarcoma (2,3). It grows rapidly in the soft tissue, but is not locally invasive or metastatic. Unpublished observations from our laboratory show that, when transplanted into bone, the tumor grows more slowly and becomes more invasive, destroying local bone by three to four weeks (see Figure 1). Recent research in cancer biology has shown that gene expression within tumor tissue is affected by the specific host environment in which it grows (4). Our hypothesis is that the bony microenvironment alters the gene expression profile of the chondrosarcoma in a time-dependent fashion, allowing it to gain invasive characteristics that it does not possess when growing in a different, soft-tissue microenvironment.

Materials and Methods: Sixty Sprague-Dawley rats underwent transplantation of SRC tissue into the tibial intramedullary space through a small drill hole and were subsequently sacrificed at 3, 7, and 21 days post-transplantation. Intramedullary tumor was removed and cryopreserved. Controls included tibiae which underwent placement of drill holes without tumor transplantation and were also sacrificed at 3, 7, and 21 days (injury group). Other controls included both native tibial bone without injury or tumor, and SRC from the soft tissue microenvironment, identical to the SRC tissue source utilized for transplantation into the experimental animals. Histology was obtained for all specimens and total RNA was extracted from each tissue sample and purified using a protocol specific for chondrocytes (1). Gene expression analysis was then performed utilizing the Affymetrix rat genome microarray. The expression patterns were analyzed using GeneSpring software.

Results: We looked specifically for genes that showed at least a 10-fold difference in expression level from the time of transplantation to the harvest at 21 days only when growing in the bone microenvironment. Interestingly, the majority of the genes that fit these criteria were sequences associated with muscle differentiation based on homology to human genes. In addition, we found time-dependent upregulation of several interesting genes in the context of cancer biology. Three of these include MMP-3, MMP-12, and beta-catenin (Figure 2). While these genes were each expressed in all samples, the levels were low and remained low over time in bone and injury controls, and they were also low in soft-tissue SRC but increased with time in SRC transplanted into the bone microenvironment.

Discussion: This experiment utilizes an animal model of chondrosarcoma of bone to study the expression profile of tumor cells in different microenvironments (soft tissue vs bone) and over time within the bone microenvironment. Genes involved in cell-matrix interaction, cell adhesion, and the Wnt signaling pathway were among those of oncologic interest that were identified, and deregulation of beta-catenin signaling is an important event in the genesis of a number of malignancies. We hypothesize that, when growing in a bone microenvironment, expression of these genes is altered, allowing local invasion and tissue destruction.

References:

This project is supported by a resident research grant from the Orthopaedic Education and Research Foundation.

Poster No: 0443