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Title: Cancer Engineering: a Translation from One Language to Another

Abstract:

Although many drugs show promise in monolayer or in animal models systems, most fail to translate in humans. In vitro, cancer cells are known to rapidly lose their cancer phenotype, while animal models often lack to recapitulate human tumors. A new generation of bioengineered tumors is now emerging in response to these limitations, with the potential to transform cancer research.

In the last five years, we have generated a set of tumor-engineered (TE) models of Ewing’s sarcoma (EWS) by using different strategies. We first described a bioengineered model of EWS that mimics the native bone tumor niche. This innovative model allows not only cross-talk between cancer cells but also between crucial bone microenvironment components, namely osteoblasts, extracellular matrix secreted by cells and native mineralized extracellular matrix. By using this approach cancer cell lines induced the expression of focal adhesion and cancer related genes highly expressed in tumors, recovered the original hypoxic and glycolytic tumor phenotype, and displayed vasculogenic mimicry features. Then, we introduced osteoclasts in the bone niche to address the role of cancer cells in osteoclasts activation during osteolysis. We observed decreases in bone volume density, bone connectivity and organic bone matrix deposition. Interestingly, the TE model recapitulated the effects of the therapeutic reagent zoledronic acid observed in patients.

We also demonstrated the utility of TE models of cancer for studies of tumor exosomes. We found that composition and stiffness of the scaffold regulated the exosomes released by the cancer cells, by mechanisms involving tensional forces. This TE model recapitulated some of the characteristics of exosomes we can observe in EWS type 1 patients, such as size and EZH2 mRNA content. Alternatively, we cultured this TE model into a mechanical loading bioreactor for better mimicking biomechanical forces in bone tumors. Interestingly, we found that biomechanical stimuli modulated anticancer drug sensitivity.