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Designer biomaterials: Too much information?

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The fields of biomaterials and tissue engineering have grown over the past decade at a breathtaking pace. Dramatic advances in biomaterials synthesis and development, biological performance evaluation, and engineering analysis have combined to cause a paradigm shift in how we use the term "biomaterials". Our concepts of how we design implants for the body now focus on integrating biological specificity, i.e., biomolecular interactions, into materials rather than trying to minimize the inevitable complications associated with commodity materials. Images in technical and lay publications that commonly showed a schematic of various organs with an assortment of artificial devices made from metal and plastic to emphasize progress in biomaterials science, now show the same functions being the targets of tissue engineering assisted by biomaterials designed to instruct cell fate.

To harness the true potential of biomimetic materials, it is imperative to assess the wound environment at the molecular level such that materials can be designed to control or redirect bone regeneration. As such, an understanding of the temporal gene and protein expression profiles during bone formation will aid in the design of materials that exploit native signals to enhance this process. Specifically, we are interested in the complete expression profile of matrix metalloproteinase (MMP)-related genes in the rat femoral ablation model so that we can better design materials to work temporally with the MMPs naturally expressed during intramembranous bone regeneration. Here, we test the hypothesis that the expression of genes of the MMP family is co-ordinated during intramembranous bone formation by determining if the temporal gene expression profiles of

MMP family ligands, as well as their regulators, are co-ordinated in the rat marrow ablation model. We observed the up regulation of MMP-13 and MMP-16 was correlated with the down-regulation of TIMP-3. Interestingly, MMP-2, MMP-14 and TIMP-2, were also co-regulated. As MMP-2 and MMP-14 play an important role in angiogenesis, and that MMP-14 activation of MMP-2 requires active MMP-14 to complex with TIMP-2 at the cell surface, suggests a rationale for the correlated action of these MMPs and TIMP-2. Furthermore, since MMP-13 was consistently up regulated, we synthesized a MMP-13 degradable artificial extracellular matrix (ECM) and assessed its bone regeneration potential.

We demonstrated that a biomimetic polymer hydrogel, that was degradable by MMP-13, was capable of affecting bone regeneration *in vivo*. Starting with a foundation consisting of an environmentally responsive poly(N-isopropylacrylamide-co-acrylic acid) hydrogel, we incorporated MMP-13 degradable cross-linkers and peptides containing integrin binding domains (i.e., Arg-Gly-Asp) to create a biomimetic matrix designed to encourage osteoblast migration and proliferation. We independently tuned matrix stiffness and peptide concentration to generate a response surface model of osteoblast proliferation on different types of matrices. Osteoblast proliferation was significantly influenced by matrix stiffness (i.e., its complex modulus) and peptide concentration. When implanted in a rat femoral ablation model, these matrices induced bone regeneration only when protease degradable cross-links were used to create the network. For the matrices with MMP-13 degradable cross-linkers, the bone formed had a trabecular-like structure and was distributed throughout the marrow space. Based on the correlated effects of matrix stiffness and ligand concentration, the response surface model will facilitate improvements in the regenerative capacity of these artificial extracellular matrices. However, a lingering question in this and other work engaging biomimetic materials is how much biological information is needed for these materials to become clinically attractive alternatives to existing technologies?

The authors have no conflict of interest.

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