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Research paper

Multiscale mechanobiology of *de novo* bone generation, remodeling and adaptation of autograft in a common ovine femur model

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ABSTRACT

The link between mechanics and biology in the generation and the adaptation of bone has been studied for more than a century in the context of skeletal development and fracture healing. However, the interplay between mechanics and biology in *de novo* generation of bone in postnatal defects as well as healing of morcellized bone graft or massive cortical bone autografts is less well understood. To address this, here we integrate insights from our previously published studies describing the mechanobiology on both *de novo* bone generation and graft healing in a common ovine femoral defect model. Studying these effects in a common experimental model provides a unique opportunity to elucidate factors conducive to harnessing the regenerative power of the periosteum, and ultimately, to provide mechanistic insights into the multiscale mechanobiology of bone generation, remodeling and adaptation. Taken together, the studies indicate that, as long as adequate, directional transport of cells and molecules can be insured (*e.g.* with periosteum *in situ* or a delivery device), biological factors intrinsic to the periosteum suffice to bridge critical sized bone defects, even in the absence of a patent blood supply. Furthermore, mechanical stimuli are crucial for the success of periosteal bone generation and bone graft healing. Interestingly, areas of highest periosteal strain around defects correlate with greatest amounts albeit not greatest mineralization of newly generated bone. This may indicate a role for convection enhanced transport of cells and molecules in modulation of tissue generation by pluripotent cells that ingress into the defect center, away from the periosteum and toward the surface of the intramedullary nail that fills the medullary cavity. These insights bring us much closer to understanding the mechanobiological environment and stimuli that stimulate the proliferation and differentiation of periosteum-derived progenitor cells and ultimately drive the generation of new bone tissue. Furthermore, these insights provide a foundation to create virtual predictive computational models of bone mechanophysiology, to develop cell seeding protocols for scale up and manufacture of engineered tissues, to optimize surgical procedures, and to develop post-surgical therapies with the ultimate goal of achieving the best possible healing outcomes for treatment and/or reconstruction of postnatal bone defects.

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1. Background

A newly described one stage bone transport procedure for segmental defect repair provides a unique healing scenario to study the multiscale (cell → tissue length scales and days → weeks → months time scales) mechanobiology of bone generation, as well as remodeling and adaptation of autograft in a common *in vivo* ovine femur model exposed to similar loading patterns among and between experimental groups (Figs. 1 and 2) (Knothe and Springfield, 2005; Knothe Tate et al., 2007; Knothe et al., 2010; Knothe Tate et al., 2010a,b). The experimental model is designed to mimic a clinical scenario in which a critical sized bone defect arises from tumor resection, traumatic injury, debridement after infection, or congenital malformation. One permutation of the model involves a single stage bone transport procedure to treat a critical sized defect (Fig. 2(A–D)) (after Knothe and Springfield, 2005); after creation of a critical sized defect (2.54 cm) in the middiaphysis of the ovine femur, periosteum proximal to the defect is peeled back and the underlying bone is osteotomized and transferred distally along the previously placed intramedullary nail to fill the defect zone. The transported bone segment is thereby denuded of periosteum and cut off from the blood supply, acting essentially as a massive bone autograft. It is anchored in place with ligament sutures and intramedullary nailing is used for mechanical stabilization. In transferring the denuded massive autograft bone distally, a new defect is created and the periosteum that was peeled back is now sutured *in situ* to envelop the new defect zone. A second permutation of the experimental model (Fig. 2(E)) involves the simple creation of a middiaphyseal, critical sized defect that is treated with a newly developed surgical reconstruction membrane in the adult ovine femur with intramedullary nailing for mechanical stabilization (Knothe Tate et al., 2010b; Knothe Tate and Knothe, 2010).

Although the first permutation of the *in vivo* model was developed primarily to provide a new method to treat critical sized long bone defects in a single index procedure, the model provides a unique means to study different aspects of bone healing after surgical reconstruction, including periosteum-derived bone regeneration in a critical sized defect (Knothe Tate et al., 2007; Knothe et al., 2010), autograft healing within the defect (Knothe Tate et al., 2007, 2010a), massive cortical autograft healing at the docking zone (Knothe Tate et al., 2010a), and periosteal regeneration in the denuded massive autograft segment (Yu et al., 2011). The second permutation of the *in vivo* model allows for periosteal substitution to elucidate effects of specific periosteal factors on *de novo* bone generation (Knothe Tate et al., 2010b; Knothe Tate and Knothe, 2010). Study of cell and tissue scale generation, adaptation and remodeling of bone within the defect zone surrounded by periosteum (Fig. 2(B)) allows for elucidation of mechanobiological effects on *de novo* bone generation by progenitor cells that reside within the periosteum. When the defect zone is filled with morcellized cancellous bone graft from the iliac crest (Fig. 2(C)), mechanobiology of autograft healing can be studied within the defect zone. Furthermore, in all groups treated using the one stage bone transport procedure, healing of a massive cortical bone autograft devoid of periosteum and vasculature (Fig. 2(D)) can be elucidated. Finally, efficacy of a novel periosteum substitute implant *cum* delivery device can be tested if the substitute periosteum is used in place of the natural periosteum to envelop the defect (Fig. 2(E)); using the modular periosteum substitute, the role of individual and combinations of periosteal factors on defect healing can be elucidated (Knothe Tate et al., 2010b; Knothe Tate and Knothe, 2010).

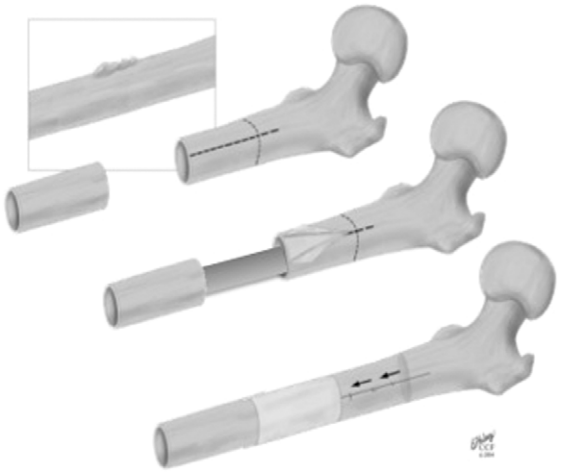

Fig. 1 – Schematic diagram of the one stage bone transport procedure after Knothe (Knothe and Springfield, 2005; Knothe Tate et al., 2007). Proximal to the defect, the surgeon gently peels back the periosteum, exposing the cortical bone beneath. The denuded section of bone is osteotomized and translocated distally to fill the original defect zone. The periosteum is sutured around the newly created defect zone. The entire construct is stabilized by an intramedullary nail.
Source: **Figure adapted from (Knothe and Springfield, 2005).**

Here we review the results of previously published studies reporting data after the so-called one stage bone transport procedure and periosteum substitution procedure; specifically, we integrate the results regarding *de novo* bone generation in the defect zone via periosteum-derived mesenchymal stem cells, defect healing in presence of morcellized autograft, healing of the massive, denuded transport segment, and optical measurement of tissue and cell scale strains in the periosteum (Knothe and Springfield, 2005; Knothe Tate et al., 2007; Knothe et al., 2010; Knothe Tate et al., 2010a,b; McBride et al., 2011a,b,c,d), in light of the current state of the art in bone mechanobiology. Our goal is to integrate insights related to the interplay between biology and mechanics in context of a common ovine model, which provides a unique opportunity to elucidate factors conducive to harnessing the regenerative power of the periosteum to generate tissue where there is none, ultimately providing mechanistic insights into the multiscale mechanobiology of bone generation, remodeling and adaptation. Our overarching hypothesis is that both proximity to factors inherent to periosteum, as well as prevailing mechanical loading patterns, modulate the generation of new bone, as well as the remodeling and adaptation of autograft, in the different healing scenarios presented by the common ovine femur surgical model.