PLATELET-DERIVED GROWTH FACTOR MODULATES DEMINERALIZED BONE MATRIX INDUCED INTRAMUSCULAR CARTILAGE AND BONE FORMATION IN IMMUNOCOMPROMISED MICE

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INTRODUCTION

PDGF is hypothesized to increase osteogenesis in orthotopic sites by simulating proliferation of osteoprogenitor cells, and in the presence of an osteoinductive material like DBM, to enhance bone healing. In vivo, PDGF is part of a natural cocktail of factors, which work together to promote tissue repair. Reddi et al (5) showed previously that addition of PDGF to DBM improved the osteoinductive properties of the DBM when implanted into old rats. The variability of commercial human DBM makes this an attractive property. The purpose of the present study was to test the hypothesis that recombinant human PDGF enhances the osteoinductive properties of human DBM.

METHODS

Human DBM (LifeNet, Inc., Virginia Beach, VA) that was previously shown to be osteoinductive in nude mouse calf muscle, was mixed with rhPDGF-BB (Biomime\textregistered
derived growth factor (PDGF), released from platelets by thrombin at a wound site, has long been implicated in healing (1). Based on this assumption, recombinant human PDGF-BB has been combined with bone allograft to treat periodontal defects (2). An alternative method of introducing PDGF into a surgical site via platelet rich plasma (PRP) has become increasingly popular (3). While the combination of bone graft material and PRP has been reported as successful (3), other studies have been less favorable (4). Many studies with PRP have been confounded by a variety of variables, including a number of bone graft substitutes and other growth factors, as well as donor variability. For this reason, we focused on a single constituent of PRP, PDGF, and used the nude mouse muscle implantation assay to examine its effects on bone formation induced by demineralized bone matrix (DBM).

RESULTS

No new bone was evident at 14 d although cartilage was present at multiple sites in tissues receiving DBM plus 0, 0.1, or 1.0 µg PDGF. Chondrogenesis was reduced >3-fold at 10 µg PDGF. By 28 d no cartilage was present in tissue with 0, 0.1, 1.0 µg/treated DBM, but it did remain in the 10 µg group. In comparison, bone formation was present at 28 d and to a similar or greater extent at 56 d. 10 µg reduced bone induction at 28 d, but this effect was resolved by 56 d. Quantitative histomorphometrics showed that the amount of new cartilage at 14 d, and of new bone and new bone marrow at 28 d were reduced in the presence of 1 µg PDGF, although the number of osteoinductive sites remained high. In sites treated with 10 µg PDGF, new bone area was decreased by 67% and area of bone marrow was reduced by 80% at 28 and 56 d. The peptide also appeared to retard DBM resorption in a dose-dependent manner, based on the area of residual DBM.

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REFERENCES


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DISCUSSION

These data suggest that lower doses of PDGF delay the induction process but do not lessen the amount of new bone formation. Only at the highest level does there seem to be an inhibition of the entire cascade. The effects of PDGF may be non-specific and may the delay the time needed for the factor to be removed from the DBM before it can become optimally inductive. If PDGF increased the pool of progenitor cells, as has been reported in soft issue wound healing, we would have anticipated delayed bone formation but ultimately a greater amount of new bone, which was not the case. The muscle muscle implantation model may have been limiting in this regard in that the amount of DBM we could use may have been insufficient to provide enough osteoinductive factors to induce chondrogenesis in an enlarged pool of undifferentiated mesenchymal cells, although PDGF was also shown to decrease bone formation induced by BMP-3 in a craniotherapy defect (6). The muscle environment may also have lacked the necessary co-factors and at the highest concentration of PDGF, cells were induced to enter other mesenchymal lineages. The difference in our results and those of Reddi et al (5) may be due to the fact that the DBM used here was a xenograft, and the model was immunocompromised mice rather than an allograft in immune competent rats. Ultimately the same amount of bone was present in all implant sites, suggesting that DBM was the over-riding factor, at least at later time points. Given that PDGF delayed bone formation at early times and did not result in increased bone formation at later times, its value as a bone graft additive may be unrelated to its effects on osteoinduction.