Effects of Salicylic Acid-Derived Poly(Anhydride-Esters) Bone Graft Barrier on Inflammation

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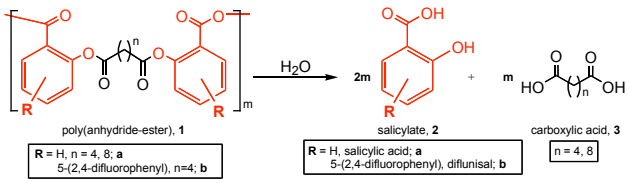
Statement of Purpose: Bioresorbable polymers offer the potential to deliver biologically active agents that can selectively modulate wound healing when used as a bone graft binder or barrier membrane for the guided tissue regeneration (GTR). For example, polymer membranes made of poly(DL-lactide) (PLA) and PLA impregnated with 4% doxycycline are currently used for GTR applications in periodontics.[1] A limitation of the PLA polymers is their exacerbation of inflammation during bioresorption and wound healing.[2] The purpose of this pilot study was to compare inflammation during early wound healing in critical-sized calvarial defects grafted with demineralized bone matrix (DBM) allograft overlaid with a barrier membrane made from a novel class of salicylic acid-derived poly(anhydride-esters) (**1**). These polymers incorporate salicylic acid (**2a**) and 5-(2,4-difluorophenyl)salicylic acid (diflunisal) (**2b**) chemically into the polymeric backbone and release the anti-inflammatory agent during resorption as outlined in Scheme 1.

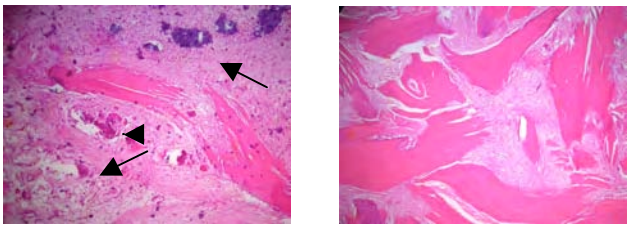


Scheme 1

Salicylic acid (**2a**) is a non-steroidal anti-inflammatory drug (NSAID) with anti-inflammatory, analgesic and antipyretic properties. Diflunisal (**2b**), a salicylate derivate, is also an effective antipyretic and anti-inflammatory analgesic known to be 7-9 times more potent as anti-inflammatory than salicylic acid and less ulcerogenic.[3-5] By incorporating these NSAID moieties into a polymer, a high load of anti-inflammatory drug (from 62 up to 82 % by weight) can be delivered.

Methods: Wound healing in response to the novel polymers (**1**), which release salicylic acid (**2a**) or the salicylic acid derivative, diflunisal (**2b**) upon degradation, was compared to grafted sites overlaid with PLA as well as sites grafted with DBM alone using paired critical-sized (5 mm) calvarial defects in 8 Wistar rats (350-450 g). NSAID-derived polymers were synthesized by melt condensation polymerization methods [6] and pressed into discs. Polymer discs (6 mm diameter x 1 mm thickness) were compared to dimensionally similar PLA polymer discs (4 defect pairs) or DBM graft alone (4 defect pairs). Defects in two additional animals served as negative controls (i.e., no graft or barrier). Animals were sacrificed at 10 or 21 days (4 each), permitting comparisons of polymers at each time period, and defects were harvested and submitted to nondecalcified processing and microscopic analysis. Inflammation was scored from 0 to 3 based on density of inflammatory cell infiltrate by an investigator masked with respect to treatment. Data were pooled to generate summary statistics but not submitted to statistical analysis, given the small sample size.

Results / Discussion: Evidence of inflammatory wound healing was found in all specimens, consistent with the post-surgical period. Grafted defects with NSAID-derived polymer discs exhibited less severe inflammatory cell infiltration (1.9 ± 0.83) than sites with DBM and PLA polymer disc (2.3 ± 0.96) or DBM alone (2.0 ± 0.82). Histopathological findings, such as foreign giant cell reaction or fibrous encapsulation, were not observed in any defects with NSAID-derived polymer. Cellular features consistent with bone formation were found in all grafted defects overlaid with NSAID-derived polymer discs at 21 days.



Representative photomicrographs of grafted defects overlaid with PLA (left) or SA-derived (right) polymer at 21 days. Inflammatory reaction is evident adjacent to residual PLA polymer (arrows).

Conclusions: These findings provide important preliminary evidence that polymers that degrade into salicylic acid (**2a**) and the salicylate derivative, diflunisal (**2b**), can function as a barrier membrane to reduce inflammation (in contrast to PLA polymer) during osseous wound healing in regenerative applications.

References:

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