Controlled delivery of GM-CSF from PLG scaffolds primes dendritic cells for the generation of anti-tumor immune responses

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Experimental cancer vaccines frequently seek to activate dendritic cells (DCs) to develop effective anti-tumor immune responses, but this approach requires the isolation, expansion, and manipulation of DCs in vitro. GM-CSF has been suggested to influence DC function, and we hypothesized that the controlled and localized presentation of GM-CSF in concert with appropriate tumor antigens would lead to an effective in vivo recruitment and activation of DCs. In vitro tests with a murine DC cell line, JAWSII, were first performed to test this hypothesis, and the results suggested that although GM-CSF enhances DC recruitment and proliferation, it also suppresses DC maturation at high concentrations (500 ng/ml), as measured by the reduced expression of the activation markers, MHCII and CCR7. To determine if similar concentration-dependent activation occurred in vivo, porous poly-lactide-co-glycolide (PLG) matrices capable of a sustained and localized release of controlled quantities of GM-CSF were fabricated and implanted into the subcutaneous pockets of C57B6 mice. This local GM-CSF delivery resulted in the recruitment and expansion of DCs in the PLG materials, increasing the number of total DCs at the implant site by as much as a factor of 12 at day 14. However, high local GM-CSF concentrations (>100 ng/ml) were also found to suppress CCR7 and MHCII expression, and to reduce emigration of the DCs to the draining lymph nodes. However, appropriate timing of GM-CSF release, and resultant local concentrations, can first allow first for the recruitment of the DCs (early high GM-CSF concentration), followed by an increase in DC maturation and the number of scaffold derived DCs in the draining lymph nodes (~-3-fold increase at days 7 and 14) as the concentration subsequently is programmed to decrease. The utility of this system as a cancer vaccine was then evaluated by incorporating melanoma tumor lysates in concert with GM-CSF in PLG scaffolds, and implanting these materials into C57B6 mice that also received B16-F10 melanoma cells. In this model, appropriate pharmacological delivery of GM-CSF was found to prevent the development tumor growth and enhanced survival by approximately 25 days. These results demonstrate that a material system allowing for control over local GM-CSF concentrations can effectively both recruit and activate host DCs to induce significant increases in anti-tumor immune responses, and thus enhance cancer vaccine effectiveness.