

Celecoxib reduces the effects of acute and chronic UVB exposure in mice treated with therapeutically relevant immunosuppressive drugs

Brian C. Wulff, Jennifer M. Thomas-Ahner, Jonathan S. Schick, Tatiana M. Oberyszyn

Department of Pathology, The Ohio State University, Columbus, Ohio

Solid organ transplant recipients have a greatly increased risk for the development of non-melanoma skin cancers. We have previously shown in our mouse model that sirolimus given in combination with cyclosporine A resulted in fewer and smaller tumors than cyclosporine A alone. In the current study, we tested the hypothesis that an anti-inflammatory agent celecoxib applied topically after UVB exposure would further reduce UVB induced skin cancer in mice treated with cyclosporine A and sirolimus. The effect of celecoxib treatment on acute inflammation, initiation/promotion and tumor development was examined through a set of four experiments. Delayed tumor onset was observed in both tumor development experiments. Reduced tumor size and number compared to vehicle was observed when CX was administered concurrently with UVB and when CX was administered after cessation of UVB treatments, respectively. Prostaglandin E2 was confirmed to be significantly reduced in the dorsal skin of mice concurrently treated with immunosuppressants, CX and UVB for 13 weeks, suggesting a reduction in the inflammatory response could be the mechanism by which CX reduced tumorigenesis. Furthermore, topical celecoxib treatment following acute UVB exposure reduced dermal neutrophil number and activity compared to vehicle. In all of these experiments, unirradiated and vehicle treated mice were utilized as controls. In conclusion, these data suggest that even in the presence of cyclosporine A and sirolimus, topical celecoxib treatment can result in reduced inflammation, tumor number and size; properties which may be beneficial in the therapeutic reduction of skin cancer development in solid organ transplant recipients.

It is becoming apparent that with more effective immunosuppressive therapies improving post-transplant survival, serious complications such as post-transplant malignancies are an increasingly important issue for transplant patients. The most common solid malignancy in transplant recipients is non-melanoma skin cancer (NMSC). NMSC is not classically thought of as a mortal disease; however, in the transplant population NMSC is more common and more aggressive than in the general population.¹⁻⁴ Often these patients present with multiple lesions in sun exposed areas known as field cancerization, which can be difficult to treat by excision, currently the standard of care. More research is needed to develop less invasive and more effective standards of care for these patients.⁵ Although the majority of research to date has focused on chemotherapeutic agents, studies examining effec-

tive chemopreventative modalities need to be explored as well.

Therapeutic immunosuppressants are used to prevent graft rejection directly and indirectly affect carcinogenesis in these patients. Cyclosporine A (CsA) is a previously favored transplant immunosuppressant that modulates the adaptive immune system through inhibition of calcineurin thus preventing activation of nuclear factor of activated T cells (NFAT). Although CsA has done much in the past to improve transplant survival, its usage is now being reevaluated due to its' multitude of side effects. Focusing on the carcinogenesis process, CsA has been shown to promote cancer development by inhibiting DNA damage repair and altering the tumor microenvironment.^{6,7} Sirolimus (SRL), also known as rapamycin, is a macrolide immunosuppressant that has been used as a therapeutic immunosuppressant and more recently as a cancer therapeutic.⁸ SRL inhibits adaptive immunity by arresting cells in the G1 phase of the cell cycle through the inhibition of mammalian target of rapamycin (mTOR).^{9,10} This same action blocks angiogenesis which along with other pro-apoptotic and anti-proliferative effects make this family of drugs potential chemotherapeutic agents.¹¹

Previous studies have shown that the combination of CsA and SRL synergistically protect against graft rejection.¹² This synergy allows for a reduction in the dose of both drugs

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Correspondence to: Tatiana M. Oberyszyn, The Ohio State University, 1645 Neil Avenue, 129 Hamilton Hall, Columbus, Ohio 43210, USA, E-mail: oberyszyn.1@osu.edu