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EDITORIAL

A refined understanding of immunosuppressives and cancer risk

Following organ transplantation a variety of immunosuppressive regimens are used to prevent acute and chronic rejection. The immunosuppressive protocols most often employ daily treatment with two or three drugs. Most often a calcineurin inhibitor is given with either mycophenolate mofetil or sirolimus or (less often) azathioprine and corticosteroids. Many centers also use poly- or monoclonal antibodies immediately following transplantation. A heightened risk for development of certain malignant diseases is an unfortunate consequence that attends the use of long-term immunosuppression [1]. While the use of potent biologic agents such as polyclonal antilymphocyte antibodies as an adjunct to standard drug therapy adds to risk of developing neoplasia, there has been no compelling evidence that the choice of any of the particular conventional drugs adds or detracts from the overall heightened risk of developing posttransplant malignant conditions resulting from the various long-term immunosuppressive regimens. However, preclinical data now suggest that it will be most important to examine the incidence of cancer in patients with respect to the particularity of the drug regimens. It seems likely that considerations in addition to the magnitude of overall immunosuppression must be considered in assessing the risk to develop and disseminate cancers and lymphomas in transplant recipients. As a prologue to the study reported in this issue of *Kidney International* by Luan et al [2], this same group has previously noted that cyclosporine (CsA) has a tumor-promoting activity linked to the drugs' ability to promote transforming growth factor-β (TGF-β) expression [3].

The paper by Luan et al [2] is a logical sequel to two other articles, one from the same group published earlier this year [4], showing that rapamycin can block tumor progression, and an article by Guba et al [5] demonstrating that rapamycin can inhibit both primary and metastatic tumor growth by antiangiogenic mechanisms. The current paper focuses on metastatic disease. The authors utilize a renal cell carcinoma pulmonary metastasis model using human renal carcinoma cells in a SCID beige mouse to evaluate the effects of rapamycin or CsA alone or rapamycin and CsA in combination on the development of pulmonary metastases and survival. CsA, a stimulant of TGF-β [3], acts to block the calcium-dependent intracellular signal resulting from activation of the T cell receptor [6] for antigen while the molecular target of the rapamycin-FKBP-12 complex is TOR, a central controller of cell growth and an important member of many growth factor signaling pathways [7].

Luan et al [2] note the effects of rapamycin on tumor cell growth, apoptosis, and the expression of two soluble factors that are known to be overexpressed in renal cell carcinoma growth, namely, vascular endothelial growth factor (VEGF-A) and TGF-β1. They find that rapamycin dramatically decreases pulmonary metastases, whereas CsA increases them and, moreover, that rapamycin reverses the CsA effect. As expected based on their earlier data [4], rapamycin arrested renal cell carcinoma cells in the G_1 phase of the cell cycle. In agreement with the publication by Guba et al [5], rapamycin diminished the expression of VEGF-A by the tumor cells. Finally, circulating VEGF-A and TGF-β1 levels were lower in rapamycin-treated mice.

There are numerous intriguing features of this study by Luan et al [2], as well as several unanswered questions. Unfortunately, the paper did not assess rapamycin levels in the blood. It would be particularly important to know if, at the doses of rapamycin utilized in vivo, the blood concentrations were below immunosuppressive levels, for example <10 ng/mL. For example, at these low levels, the authors have previously shown striking effects on proliferation of renal cancer cells in vitro. Also unanswered is the question of how pertinent this effect is in malignant diseases other than renal cell carcinoma, although the paper by Guba et al [5] utilized a colon cancer line and early papers have used several other lines [8, 9]. Thus, the question of whether renal cell cancers are particularly susceptible to rapamycin inhibition needs to be addressed in future studies. Of note, the rapamycin analog CCI-779 is showing some activity in advanced renal cell carcinoma in early studies (abstract #36; Atkins MB et al, ASCO 2002 Meeting).

The mechanisms by which rapamycin exerts effects on both the tumor and on the endothelial cell compartments in a cancer warrant more investigation. Clearly, there are effects on cell-cycle progression in the tumor cell and rapamycin can also reverse, in part, the mesenchymal phenotype of invasive tumor cells, as shown by its ability to induce E-cadherin in renal cancer cells [4]. However, little is known of the detailed signaling involved in this process. Rapamycin also blunts VEGF and TGF-β1 intracellular signaling effects. The authors have not assessed a third cytokine that is also well known to be up-regulated

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in renal cell carcinoma, namely, TGF-α, against which therapies are being designed in renal cell carcinoma [10]. In renal cell carcinoma, over 80% carry mutation or hypermethylation of the von Hippel-Lindau (VHL) tumor suppressor gene, resulting in stabilization of hypoxia-inducible factor-1a (HIF-1a) and subsequent overexpression of VEGF-A, TGF-β1, and TGF-α [10]. A unifying hypothesis to explain this data would be to position mTOR upstream of HIF-1a, and downstream of activation of numerous receptor kinases and hypoxia. Several recent observations support this thesis [11–14].

Finally, the effects of rapamycin on the endothelial cell merit further investigation. For VEGF and angiopoeitin to support the survival and migration of endothelial cells, signaling via phosphatidylinositol 3′ (PI3)-kinase (an upstream activator of mTOR via Akt) is clearly important [15, 16]. The role of this pathway in mediating other pro-angiogenic cytokine signals needs to be elucidated. Finally, it will be of great importance to carefully examine transplant registry data for evidence to support or refute the notion that the use of CsA promotes and sirolimus retards the propensity to develop posttransplant neoplasia.

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