by modulation of TSC1/2, a proximal upstream regulator of mTOR (see figure). These data give a clear rationale to pursue existent mTOR inhibitors, including RAD001, CCI-779, and AP23573, possibly in combination with Bcl-2 inhibitors, in patients with follicular lymphoma.[1] Many of our current kinase inhibitors have a much broader range of inhibitor activity than is initially focused on in the clinic.[5] A screen of currently available kinase inhibitors for Syk inhibitor activity and the development of specific Pim and Syk inhibitors is indicated.

The author declares no competing financial interests. ■

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NEOPLASIA

Comment on Moreaux et al, page 4194

No tumor-CD200 expression, please!

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This issue of *Blood* features a study suggesting that cancer patients whose myeloma cells express the molecule CD200, which is known to have important immunoregulatory properties, have a poorer prognosis than patients with CD200$^-$ tumors.

Intense interest has recently centered around the identification, using microarray technology, of novel molecules that might have a diagnostic and/or prognostic role in helping researchers to understand tumor growth and development. Other groups have used more conventional model-driven approaches to explore the possibility that interference with known immunoregulatory or inflammatory pathways is correlated with tumor-host interactions. Independently, these 2 approaches have identified a potential role for expression of the molecule CD200 on tumor cells in resistance to tumor growth.[1,2] The paper by Moreaux and colleagues in this issue of the journal provides further support for this hypothesis with the provocative demonstration that myeloma CD200 expression identifies a patient population with poorer long-term prognosis than individuals with low CD200 expression.

CD200 is a relatively ubiquitously expressed type 1 transmembrane glycoprotein, which, lacking signaling domains or adapter motifs for other signaling molecules, is thought to interact with CD200Rs expressed on myeloid cells/lymphocytes and alter their function. There is a correlation between CD200 overexpression and suppressed immunity that is abolished by anti-CD200 antibody and restored by a fusion protein linking the extracellular domain of CD200 to the Fc region of IgG2a, CD200Fc.[3] Additional studies have implied a more general role for CD200:CD200R interactions in regulation of a number of immune states, including autoimmunity, fetal loss syndrome, transplant rejection, tumor immunity, infection, and allergy.[3]

There are a number of intriguing aspects of CD200-CD200R biology within whose framework the study by Moreaux et al must be considered. It has become apparent that all CD200Rs are not the same, and that while CD200 engagement of CD200R1 delivers a direct immunoregulatory signal to R1$^+$ cells, engagement of non-CD200R1 (alternate) receptors may activate a different intracellular signaling pathway, resulting in immunoregulation through different mechanisms.[3] In experimental systems, engagement of alternate CD200Rs induces tolerogenic dendritic cells that activate CD4$^+$CD25$^+$ regulatory T (Treg) cells,[3] already implicated by a number of groups in host resistance to infection, autoimmunity, and malignancy. The avidity of soluble forms of alternate CD200Rs for CD200 is significantly less than that of CD200R1, and it has been suggested that alternate CD200Rs are triggered by ligands other than CD200.[4] At this time, the antitumor effects of triggering alternate CD200Rs in humans are unknown. Thus, among the mechanisms explaining a failure to control tumor growth subsequent to augmented CD200 tumor expression, one could postulate a direct immunosuppression following engagement of CD200R1 on effector cells (T cells and/or macrophages) or alternatively even induction of increased Treg cells secondary to triggering of alternate CD200Rs. The therapeutic effect of blocking CD200 expression, an approach suggested to have value in model systems,[2] and even in human lymphoma,[1] may differ depending upon which mechanism(s) is important. The study by Moreaux et al does report that at least in the marrow environment, there was no evidence for CD200 overexpression on various resident host cell populations, although expression of CD200Rs was not investigated. Future research will hopefully address whether measuring CD200R expression provides additional valuable information, and indeed the mechanism(s) whereby CD200 expression foretells a poor prognosis.

The author holds a "use patent" granted (in association with Trillium Therapeutics Inc) for CD200 in autoimmunity and transplantation. ■

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