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Comment on Frost et al, page 4181, and comment on Raje et al, page 4188

Toward a rational combinatorial therapy for multiple myeloma

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The phosphatidylinositol 3-kinase/Akt (PI3-K/Akt) signaling pathway regulates growth and survival in multiple myeloma (MM) in vitro. Of the many substrates regulating caspase activity and apoptosis downstream of Akt, the mammalian target of rapamycin, mTOR, has been thought to act as a special survival checkpoint kinase in several cell types. In 2 articles appearing in this issue of *Blood*, such a function has now been ascribed to mTOR also in MM cells in vivo.

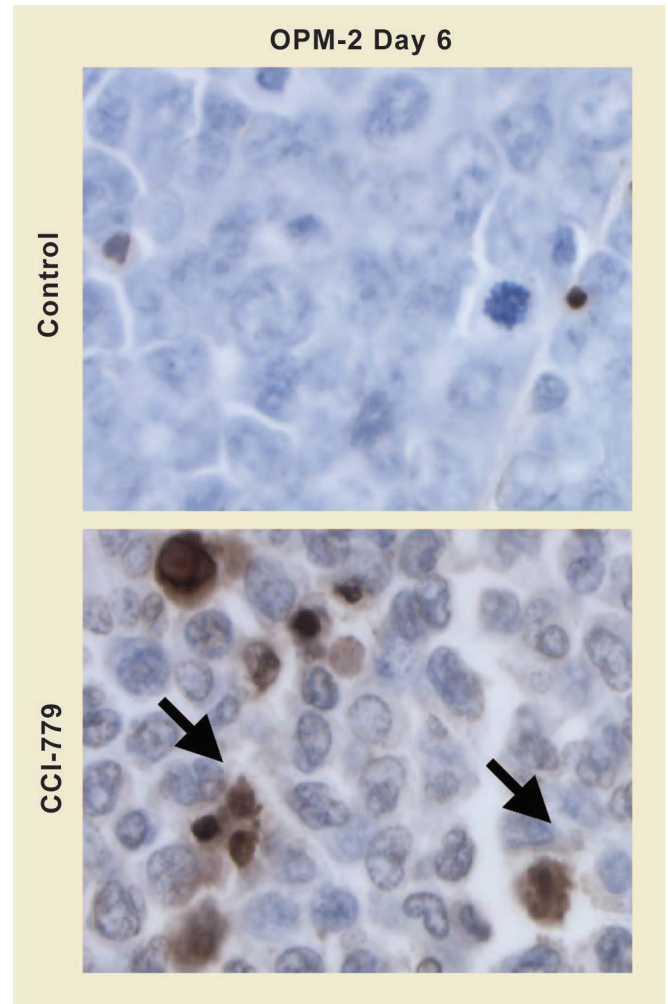
Multiple myeloma (MM) is genetically and clinically a highly heterogeneous disease characterized by the expansion of slow-growing, and relatively apoptosis-insensitive, malignant plasma cells in the bone marrow.¹ The bone marrow microenvironment provides growth stimulatory signals (eg, insulin-like growth factor-1 [IGF-1] and interleukin-6 [IL-6]) to the tumor cells. Molecules within the IGF-I receptor (IGF-IR)/phosphatidylinositol 3-kinase/Akt (PI3-K/Akt) signaling pathway, regulating preferentially survival/death, may therefore serve as important targets for therapy.

mTOR is a protein Ser-Thr kinase with key substrates involved in protein synthesis.² Although the antineoplastic effect of rapamycin was known 20 years ago, the discovery of mTOR unleashed its potential anticancer activities. Previous in vitro studies have indicated its therapeutic potential in MM, and suggested that the constant or elevated Akt activity may be a major predictor of sensitivity to mTOR inhibitors.³⁻⁵

Frost and colleagues now confirm their previous findings in vitro and show that the rapamycin ester analog CCI-779 induces significant reduction of subcutaneous growth of MM cell lines in a mouse immunodeficiency model. The finding of induced apoptosis was somewhat surprising, since exposure to CCI-779 in vitro has only cytostatic effects. A possible explanation for this finding is an indirect angiogenic effect of CCI-779. The correlation between phosphatase and tensin homolog de-

leted on chromosome ten (PTEN) mutations, increased Akt activity, and high sensitivity to mTOR inhibitors observed in vitro turned out to be valid also in their mouse model of MM. The PTEN-mutated cell line was considerably more sensitive to CCI-779. However, 3 to 4 weeks after treatment, approximately 75% of the tumors reappeared and grew regardless of PTEN status.

A parallel paper by Raje and colleagues in this issue of *Blood* supports the notion that anticancer therapy will be more effective when drugs are combined rationally to target distinct apoptosis-inducing signaling pathways. CC-5013 (Revlimid), a thalidomide analog, and rapamycin displayed synergistic antitumor effects in vitro. The clinical benefit of this combinatorial treatment is obviously that the combination of rapamycin and CC-5013, in contrast to the cytostatic effects observed by rapamycin alone, induces apoptosis at doses well below those pharmacologically achievable in vivo. Further implicating its in vivo potential, this treatment may override drug resistance and growth advantage conferred by multiple factors provided by the bone marrow environment. The specific downstream effec-



CCI-779 induces myeloma cell apoptosis. See the complete figure in the article beginning on page 4181.

tors of rapamycin- and CC-5013-induced apoptosis are, however, not fully detailed. One plausible and very attractive mechanism is that the combinatorial treatment targets survival pathways activated in parallel by one or several growth factors.

Although mTOR inhibitors have shown promising effects in preclinical studies, CCI-779 treatment has so far resulted in only modest responses in phase 2 studies, and have not yet been performed in MM. The clinical benefit of a combinatorial treatment was also recently suggested by the finding that rapamycin combined with conventional drugs (ie, dexamethasone, doxorubicin, or melphalan) induced apoptosis in MM cell lines and biopsies in vitro.³ Taken together, the studies by Frost et al, Raje et al, and Stromberg et al³ suggest that successful future treatment

regimens of MM should be individualized and include a rational combination of drugs targeting select molecules of predominating survival- and growth-regulatory pathways, genetically deregulated or merely stimulated by the bone marrow microenvironment. ■

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IMMUNOBIOLOGY

Comment on Herre et al, page 4038

Dectin-1: unique appetite for yeast

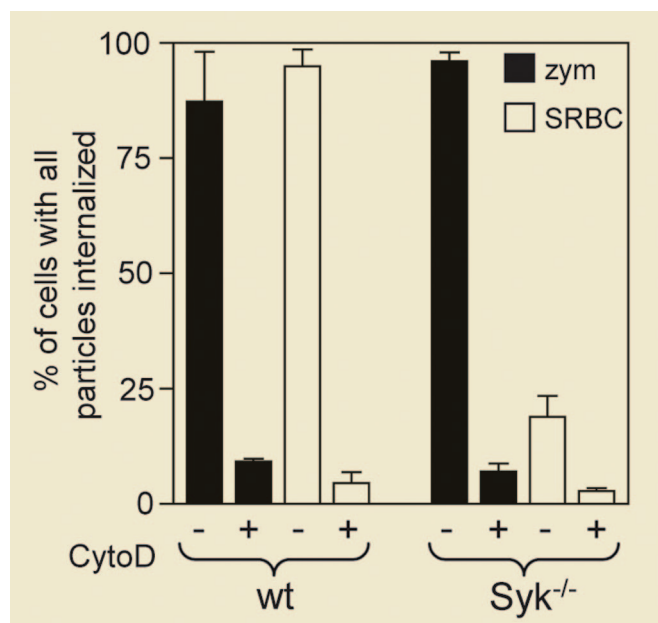
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Dectin-1 is a myeloid receptor involved in phagocytosis of fungal pathogens that uses a unique mechanism of internalization and cellular signaling.

Phagocytosis of pathogens is a critically important activity of cells of the innate immune system. Professional phagocytes, such as macrophages, are equipped with a wide array of cell surface receptors, which are either directly or indirectly involved in recognition, uptake, and presentation of these antigens, as well as cellular signaling. The indirect receptors, such as Fcγ receptor (FcγR) and complement receptors, are well characterized and recognize pathogens opsonized with immunoglobulins and active

complement fragments.¹ Signaling via FcγR is especially well established and involves the associated common gamma chain, which bears an immunoreceptor tyrosine-based activation motif (ITAM) critical for this activity. In addition, professional phagocytes/antigen-presenting cells express direct pattern recognition receptors, many belonging to the C-type lectin family, including macrophage mannose receptor (CD206) and scavenger receptor, but also receptors specific for dendritic cell subsets

such as DC-SIGN (CD209), Langerin (CD207), DEC-205 (CD205), and BDCA2.² Dectin-1 is another receptor broadly expressed on myeloid cells belonging to this family that recognizes β-glucan structures, such as those exposed on the outside of fungal pathogens.³ Interestingly, this receptor combines the extracellular lectin domain with an intracellular region reminiscent of an ITAM motif. A study by Herre and colleagues in this issue of *Blood* further unravels the intracellular



Comparison of Dectin-1 and FcγR-mediated phagocytosis in macrophages, demonstrating that Dectin-1-mediated phagocytosis is Syk-independent.

lar mechanisms of Dectin-1-mediated phagocytosis. Using transfected 3T3 fibroblasts, the critical contribution of the ITAM motif was demonstrated. Intracellular truncation or point mutation in the membrane proximal tyrosine residue did not affect binding, but hampered phagocytosis of yeast particles. The use of pharmacologic inhibitors also suggested that Dectin-1-mediated and FcγR-mediated signaling followed a similar process. However, major differences were found when studies were performed in either RAW macrophages, transduced with the Dectin-1 receptor, or freshly isolated macrophages. For FcγR signaling, the Syk kinase is a pivotal component,⁴ as confirmed by the authors showing the inability of macrophages from Syk^{-/-} mice to take up opsonized sheep red blood cells. However, the same cells were fully competent in Dectin-1-mediated internalization (see figure). Herre et al went one step further and investigated whether the intracellular trafficking of the Dectin-1 receptor was affected by the nature of the ligand. The uptake of large particles was associated with a re-expression of the receptor completely dependent of de novo protein synthesis. However, smaller β-glucans, such as laminarin, showed a receptor recycling independent of protein synthesis. It is conceivable that this difference has major implications for the antigen-presentation process and deserves further attention. Moreover it will be interesting to study these processes in the different myeloid cells expressing Dectin-1. Finally, the results of Herre et al raise the question of whether other cellular processes initiated by Dectin-1 triggering, such as production of inflammatory mediators, are also determined by the nature of the recognized ligand. ■

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