

blood

2005 106: 395-
doi:10.1182/blood-2005-04-1578

New aspects of myeloma management

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ICAM-1 is necessary for its function in modulating neutrophil-endothelial interactions. Although the mechanism is still not clear, ligation of endothelial ICAM-1 by LFA-1 likely results in ICAM-1–mediated signaling that leads to cytoskeleton changes and leukocyte TEM.⁴

Not only did the authors find that the surface density of ICAM-1 is important in regulating transcellular migration, but they observed that the shape of endothelial cells played a role in determining the migration route of PMNs. Comparison of PMN migration across ICAM-1GFP–transfected and control endothelial monolayers revealed that endothelial cells with polygonal morphology appeared to promote nonjunctional arrest and transcellular migration. Interestingly, polygonal endothelial cells with high-density expression of ICAM-1 and VCAM-1 have been identified in locations with high predilection for atherosclerosis in both rabbit and mouse models of atherogenesis.⁵ It is thus likely that these conditions (high density of ICAM-1 and polygonal endothelial cell shape) might support a high ratio of transcellular to paracellular TEM and contrib-

ute to disease pathogenesis. Another interesting point from this study was that T lymphocytes, unlike neutrophils, do not migrate via transcellular mechanisms even under conditions of increased ICAM-1 expression. Future in vitro studies are needed to determine if TEM of monocytes is similar to that observed for PMNs or T lymphocytes. ■

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● ● ● NEOPLASIA

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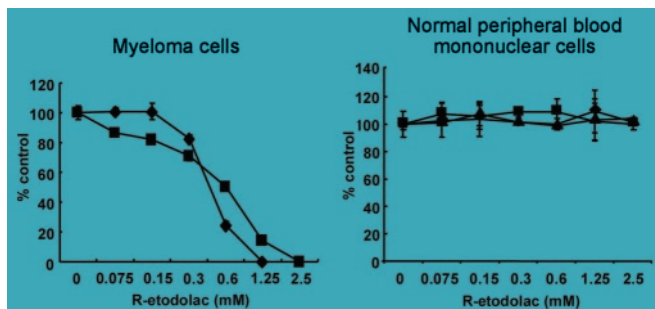
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SDX-101, the etodolac R–enantiomer, is an anti-inflammatory drug with a cytotoxic effect on multiple myeloma cells but not on normal peripheral blood mononuclear cells.

The antiproliferative activity of nonsteroidal anti-inflammatory drugs and their potential use as antitumor agents are under scrutiny.¹ A starting point is the demonstra-

tion that these drugs have some effects on cancer cells.

In this issue of *Blood*, Yasui and colleagues provide the first evidence of the cytotoxic effect of SDX-101, the R–enantiomer of etodolac, in different multiple myeloma (MM) cell lines. The authors illustrate SDX-101's antitumor activity against both drug-sensitive and –resistant MM cells and against primary patient MM cells within the bone marrow



SDX-101 induces growth inhibition in MM cell lines. See the complete figure in the article beginning on page 706.

environment. It is important to bear in mind that these effects were obtained with concentrations without cytotoxicity on normal peripheral blood mononuclear cells and at clinically achievable plasma levels.

Some MM cells were resistant to doxorubicin, dexamethasone, and bortezomib and were hence highly hypermutated. The cytotoxic effect is mediated via caspase-8/-9/-3 activation and apoptosis. In addition, SDX-101 induced down-regulation of cyclin D1 expression in MM cells, resulting in an apoptotic population, as shown by cell-cycle analysis.

As they have previously shown that novel chemotherapeutic agents augment the cytotoxicity of dexamethasone,² Yasui and colleagues now demonstrate that the combination of SDX-101 plus dexamethasone is highly synergistic. It has been well established that myeloid cell leukemia-1 (Mcl-1) plays an important role in proliferation and inhibition of apoptosis, as well as in the induction of drug resistance³: the results obtained by Yasui and colleagues thus strongly suggest that up-regulation of the proapoptotic variant Mcl-1_S and inhibition of the antiapoptotic variant Mcl-1_L are the principal events in the apoptotic activity of SDX-101.

It has previously been reported that the bone marrow microenvironment plays an important role in the pathogenesis of MM.^{4,5} Yasui and colleagues demonstrate that SDX-101 ablates the growth stimulatory effect of this microenvironment on MM cells. It is interesting to note that SDX-101 lacks cyclooxygenase (COX) inhibitory activity and hence the related side effects and that it is approved for treatment of degenerative joint diseases and rheumatoid arthritis. Results as a whole provide the preclinical framework for clinical trials of SDX-101 alone or in combination with dexamethasone to improve patient outcome in MM. The study is an important contribution to MM research. ■

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