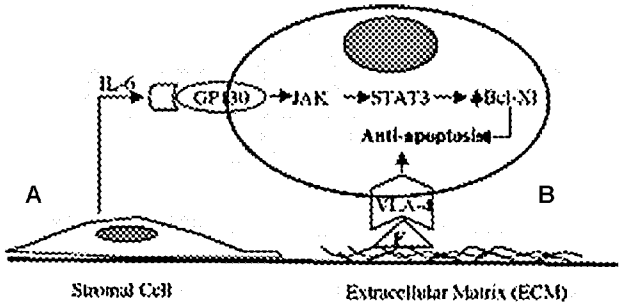
469 INVITED

Environmental mediated drug resistance (EMDR) in hematologic malignancies

W.S. Dalton. *H. Lee Moffitt Cancer Center, University of South Florida, Tampa, USA*

Classically, studies of drug resistance in cancer have focused on the molecular biology of single cancer cells. These types of studies have provided important information regarding acquired drug resistance mechanisms, including mechanisms that reduce intracellular drug accumulation, alter or repair drug-induced damage, and reduce drug-induced apoptosis. Acquired drug-resistant models have been critical in elucidating intrinsic drug-resistant mechanisms; however, these models do not consider resistance mechanisms elicited by extrinsic influences such as the tumor microenvironment. We propose that the tumor microenvironment provides a sanctuary for subpopulations of tumor cells to evade or circumvent drug-induced death and that this represents a form of de novo drug resistance. Furthermore, this extrinsic form of de novo drug resistance contributes to minimal residual disease (MRD) resulting in the emergence of acquired drug resistance. We have found that elements of the bone marrow microenvironment, including extracellular matrices and stromal elements, protect hematologic malignant cells from drug-induced cell death. We propose that environmentally mediated drug resistance (EMDR) protects tumor cells from stress and cell death by two mechanisms: (A) a paracrine mechanism due to soluble cytokine factors produced as a result of the tumor cell:environment interaction, and (A) a physical contact mechanism we have termed "cell adhesion mediated drug resistance (CAM-DR)".



Two different forms of tumor–microenvironment interactions influence drug response in cancer.

Our initial studies comparing genotypic and phenotypic profiles of drug resistance indicate that EMDR is less complex compared to acquired drug resistance. Focusing on EMDR may reduce MRD and prevent the emergence of acquired drug resistance in hematologic malignancies. Two different forms of tumor cell-environmental interaction may explain how some tumor cells survive initial drug exposure and eventually express classical mechanisms of drug resistance. The first form involves soluble mediators, such as interleukins, that are secreted by non-tumor, stromal cells. Interleukin-6 (IL-6) is a classical example of how a soluble mediator secreted by the tumor microenvironment is capable of enhancing tumor cell survival and perhaps blocking apoptosis. The second form of tumor cell-environment interaction requires direct cell contact and has been given the term cell adhesion mediated drug resistance. In this case, binding extracellular matrix ligands, and bone marrow stromal elements in the tumor microenvironment may activate cell adhesion molecules, such as the integrins, and these interactions result in the activation of signal transduction pathways that block drug-induced apoptosis. Our work, as well as the work of others, have shown that the signaling pathways involved in EMDR are cell lineage, as well as, environmentally dependent. Interrupting the tumor cell-environment interactions or the associated signal transduction pathways may represent a new approach for the treatment of cancer by preventing MRD and the emergence of acquired drug resistance.

References

Damiano JS, Cress AE, Hazlehurst LA, Shtil AA, Dalton WS. Cell adhesion mediated drug resistance (CAM-DR): Role of β_1 integrins and resistance to apoptosis in human myeloma cell lines. Blood 93:1658–1667, 1999.

Hazlehurst L, Damiano J, Buyuksal I, Pledger WJ, Dalton WS. Adhesion to fibronectin via β 1 integrins regulates $p27^{kip1}$ levels and contributes to cell adhesion mediated drug resistance (CAM-DR). Oncogene 19:4319–4327, 2000.

Hazlehurst L, Valkov N, Wisner L, Storey J, Boulware D, Sullivan D, Dalton WS. Reduction in drug-induced DNA double-strand breaks associated with β 1 integrin-mediated adhesion correlates with drug resistance in U937 cells. Blood Sep 15;98(6):1897–903, 2001

Shain K, Landowski T, Dalton WS. Adhesion-mediated intracellular redistribution of c-fas-associated death domain-like IL-1-converting enzyme-like inhibitory protein-long confers resistance to CD95-induced apoptosis in hematopoietic cancer cell lines. Journal of Immunology, 168:2544–2553, 2002.

Nefedova Y, Landowski TH, Dalton WS. Bone marrow stromal-derived soluble factors and direct cell contact contribute to *de novo* drug resistance of myeloma cells by distinct mechanisms. Leukemia 17:1175–1182, 2003.

Landowski TH, Olashaw NE, Agrawal D, Dalton WS. Cell Adhesion Mediated Drug Resistance (CAM-DR) is Associated with Activation of NF-κB (RelB/p50) in Myeloma cells. Oncogene 22:2417–2421, 2003.

Hazlehurst LA, Enkemann SA, Beam CA, Argilagos RF, Painter J, Shain KH, Saporta S, Boulware D, Moscinski L, Alsina M, Dalton WS. Genotypic and Phenotypic Comparisons of *de-novo* and Acquired Melphalan Resistance in an Isogenic Multiple Myeloma Cell Line Model. Cancer Research 63: 7900–7906, 2003.

Nefedova Y, Cheng P, Alsina M, Dalton WS, Gabrilovich DI. Involvement of Notch-1 signaling in bone marrow stroma-mediated de novo drug resistance of myeloma and other malignant lymphoid cell lines. Blood 103(9): 3503–3510, 2003.

Friday 1 October

Poster Sessions

Anthracyclines

470 POSTER

Efficacy of nemorubicin (MMDX) administered with iodinated oil via hepatic artery (IHA) to patients with unresectable primary hepatocellular carcinoma (HCC): phase II trial

Y. Sun[1], J. Yang[2], P. Luo[3], Y. Zhang[4], Y. Yan[5], L. Sun[5], M.A. Pacciarini[6], O. Valota[6], C. Geroni[7]. *[1]Cancer Hospital, Chinese Academy of Medical Sciences, Oncology, Beijing, China; [2]First Affiliated Hospital, Sun Yat-Sen University of Medical Science, Oncology, Guangzhou, China; [3]Guangdong Provincial Peoples Hospital, Oncology, Guangzhou, China; [4]Cancer Hospital, Zhongshan University, Oncology, Zhongshan, China; [5]Pfizer, Oncology, Beijing, China; [6]Nerviano Medical Science, Clinical Oncology, Nerviano, Italy; [7]Nerviano Medical Science, Biology, Nerviano, Italy*

MMDX is a doxorubicin (DX) derivative with different mode of action, superior therapeutic activity including activity on multidrug resistance tumor models and improved tolerability (mainly reduced cardiotoxicity relative to DX). The past clinical experience by IV route evidenced a special affinity of MMDX for liver lesions, whose regression in pts with colorectal, renal, breast cancer were reported in Phase (Ph) I-II studies (Vasey, Cancer Res, 1995; de Takats, Proc ECCO 9, 1997). The specific antitumor activity may be due to the formation of highly cytotoxic metabolite(s) by liver enzymes. These findings prompted to test the efficacy of MMDX by IHA in HCC. Ph I studies were conducted in EU and in China. The encouraging efficacy and safety results (Sun, ASCO, 2003) were supportive of continuing the development in HCC.

A registrative ph II/III randomized study was started in China in 2002, with MMDX administered by IHA in iodinated oil at 600 mcg/m^2 every 6 weeks to chemotherapy-naïve pts with unresectable HCC.

27 pts [25 male and 2 female (mean age 51.5, range 35–68 years); ECOG-PS 0 (21 pts) or 1 (6 pts); AJCC stage II (8 pts) and IIIA (19 pts); median number of cycles 2 (range 1–5)] were treated in the first stage of the Ph II portion of the study. 24 pts are currently evaluable for efficacy.

Partial remissions (PRs), evaluated by the WHO criteria occurred in 5/24 pts (4 confirmed) (RR = 20.8%; 95% c.i.: 7.1–42.2%).

Mild/moderate reversible neutropenia was reported in a small number of pts. Thrombocytopenia (Gr 3) occurred in 15% of pts (some pts were already thrombocytopenic at baseline). A mild/moderate SGOT/SGPT reversible increase occurred in 48% and 61% of cycles, respectively (max Gr 3 increase in 16% and 9.4% of cycles for SGOT and SGPT, respectively). No Gr 4 increase and no trend to cumulative liver toxicity with repeated administrations (neither in severity nor in frequency) were reported. Nausea and vomiting were also observed (Gr 3 vomiting in 11% of pts), being however mild/moderate in severity and resolving spontaneously in most cases without requiring antiemetic treatments. All the episodes recovered within 1 week. No Gr 4 gastrointestinal toxicity was observed.