How to develop better screens for anti-cancer therapies?

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The clinical efficacy of chemotherapy relies in part on its ability to potentiate anti-tumor immune responses. Recent work shows that several chemotherapeutic drugs induce intra-tumoral expression of lymphocyte-attracting chemokines, leading to clinical responses. Here, we argue that such knowledge should be used to screen for novel anti-tumor treatments.

Currently approved chemotherapeutic drugs are initially screened in vitro for their capacity to induce cell death in cancer cell lines. Before being used in patients, these drugs have to be tested in various preclinical models and in lengthy and costly human trials to demonstrate a clinical benefit. Unfortunately, the rate of new drug failure at the clinical stage is very high: the attrition rate of drugs developed by large pharmaceutical companies has recently been estimated at around 93%. Very few drugs initially showing promising activity in vitro are eventually approved, illustrating the shortcomings of the current cell line assays and preclinical models. We must seek something better.

Tumors are not only made of cancer cells; the role of the stroma in tumor growth and metastasis is well known. In particular, the importance of the immune microenvironment is increasingly recognized. The nature, number, localization and polarization of immune cells infiltrating human tumors are among the strongest predictors of patient survival. Immune cells are involved in many steps of cancer progression including tumor growth, invasion, dissemination and colonization of distant organs. For example, defined subsets of tumor-associated macrophages produce growth factors and promote angiogenesis. Myeloid-derived suppressor cells (MDSC) prevent T-cell activation and induce epithelial-mesenchymal transition, thereby favoring growth of the primary tumor and facilitating cancer cell dissemination. Immune cells also play a major role in controlling cancer progression by inducing cancer cell death or favoring tumor dormancy. It is therefore not unexpected that the ability of drugs to control cancer progression in patients relies, in part, on their effect on immune cells. Unfortunately this aspect is not addressed in the in vitro assays or xenograft models commonly used to screen chemotherapeutic drugs.

Until recently, the prevalent view was that chemotherapy merely blunts the immune response. Indeed, most chemotherapies do induce bone marrow depletion; tamoxifen, cisplatin, carboplatin or temozolomide induce leucopenia and/or thrombocytopenia. But recent data also revealed that chemotherapies can have beneficial effects on the anti-tumor immune response. First, chemotherapeutic drugs can potentiate the induction of an immune response. Low doses of cyclophosphamide deplete or inhibit regulatory T cells (Treg), while gemcitabine or 5-fluorouracil selectively eliminate MDSC. Some chemotherapeutic drugs induce immunogenic death, a process in which debris from dying cancer cells is captured by dendritic cells which stimulate the induction of an anti-tumor immune response. Second, some drugs improve lymphocyte effector functions and act in synergy with immune cells, making cancer cells more sensitive to immune effectors. For example, genotoxic drugs trigger the DNA-damage response and augment NKG2D ligand expression, which facilitates cancer cell recognition by NK and T cells.

We recently uncovered a third extrinsic mode of action of chemotherapy (Fig. 1). In melanoma patients, dacarbazine induced intra-tumoral expression of T and NK cell-attracting chemokines (CXCL9, CXCL10 and CCL5). While before treatment, immune effectors largely ignored cutaneous tumors, a significant lymphocytic infiltrate was observed in the cutaneous tumors after chemotherapy. Importantly, this was only observed in tumors responding to the treatment. No chemokine expression was induced by dacarbazine in chemotherapy-resistant tumors. Moreover, patients in whom dacarbazine induced increased expression of these chemokines survived longer. Experiments performed in mice showed that CXCR3, the receptor for CXCL9 and CXCL10 expressed on circulating effector T cells, was required for chemotherapy-induced infiltration of T cells. In vitro experiments confirmed that several chemotherapeutic drugs induced expression of CXCL9,
CXCL10 and CCL5 in many cancer cell lines.

It may seem paradoxical for cancer cells to express chemokines that attract cancer cell-killing lymphocytes. However, chemokine expression is probably a physiological response of normal cells to stress. This interpretation is confirmed by our recent finding that intra-tumoral expression of CXCR3 ligands and CCL5 in hepatocellular carcinoma (HCC) samples correlates with higher infiltration of T and NK cells and prolonged patient survival. In fact, normal hepatocytes do express these chemokines in response to inflammation. Therefore, the beneficial effects of chemotherapies are, in part, linked to their action on immune cells, and this situation is not unique to conventional chemotherapy. Imatinib mesylate (Gleevec) was initially approved in 2001 for its capacity to inhibit the tyrosine kinase BCR-ABL in chronic myeloid leukemia (CML). Gleevec was later found to inhibit another tyrosine kinase, c-kit. Because the vast majority of gastrointestinal stromal tumors (GIST) contain an activating KIT mutation, this drug was then used in GIST. But a recent study showed that Gleevec’s efficacy in GIST relates primarily to its capacity to inhibit the immunosuppressive enzyme indoleamine 2,3-dioxygenase (Ido) and thereby to potentiate T cell responses.

We are just starting to understand how drugs work in cancer patients. Clearly, the biological events leading to clinical responses in patients often differ from the mechanisms for which the drug was initially selected and developed. It is essential to incorporate this knowledge in the assays used to screen new drugs. In particular, we should develop assays aimed at identifying which drugs act on the immune system and favor immune cell trafficking to the tumor. It would also be useful to test currently approved drugs in such assays. Better assays would increase the chance of success in clinical developments.

References
1. Bunnage ME. Getting pharmaceutical R&D back on target. Nat Chem Biol 2011; 7:335-9; PMID: 21587251; http://dx.doi.org/10.1038/nchembio.581
2. Fridman WH, Galon J, Dieu-Nosjean MC, Cremer I, Fisson S, Danotte D, et al. Immune infiltration in human cancer: prognostic significance and disease control. Curr Top Microbiol Immunol 2010; 344:1-24; PMID:20512556; http://dx.doi.org/10.1007/82_2010_46
3. Porta C, Suhbha Kumar B, Laugi P, Rubino L, Mancino A, Sica A. Tumor promotion by tumor-associated macrophages. Adv Exp Med Biol 2007; 604:67-86; PMID:17695721; http://dx.doi.org/10.1007/978-0-387-69116-9_5
4. Tab B, Wang X, Keeble J, Sim WJ, Khooh K, Wong WC, et al. Mesenchymal transition and dissemination of cancer cells is driven by myeloid-derived suppressor cells infiltrating the primary tumor. PLoS Biol 2011; 9: e1001162; PMID:21980265; http://dx.doi.org/10.1371/journal.pbio.1001162
5. Anderson BO, Austin-Seymour MM, Gralow JR, Moe RE, Byrd DR. A Multidisciplinary Approach to Locoregional Management of the Axilla for Primary Operable Breast Cancer. Cancer Control 1997; 4:491-9; PMID:10763057
6. Zitvogel L, Kepp O, Kroemer G. Immune parameters affecting the efficacy of chemotherapeutic regimens. Nat Rev Clin Oncol 2011; 8:151-60; PMID:21364608; http://dx.doi.org/10.1038/nrclinonc.2010.223
7. Gasser S, Rauler D. The DNA damage response, immunity and cancer. Semin Cancer Biol 2006; 16: 344-7; PMID:16914325; http://dx.doi.org/10.1016/j.semcancer.2006.07.004
8. Hong M, Paauw AL, Huang C, Louamgine L, Tow C, Mackay C, et al. Chemotherapy induces intratumoral expression of chemokines in cutaneous melanoma, favoring T cell infiltration and tumor control. Cancer Res 2011; 71:6997-7009.
9. Chew V, Chen J, Lee D, Loh E, Lee J, Lim KH, et al. Chemokine-driven lymphocyte infiltration: an early intratumoural event determining long-term survival in resectable hepatocellular carcinoma. Gut 2012; 61:427-38; PMID:21930732; http://dx.doi.org/10.1136/gutjnl-2011-300509
10. Balachandran VP, Cavnar MJ, Zeng S, Bambout ZM, Oceans LM, Ohaid H, et al. Imatinib potentiates antitumor T cell responses in gastrointestinal stromal tumor through the inhibition of Ido. Nat Med 2011; 17:1094-100; PMID:21873989; http://dx.doi.org/10.1038/nm.2438

Figure 1. Newly discovered mode of action of chemotherapy. Chemotherapy induces melanoma cells to express chemokines (CXCL9, CXCL10 and CCL5) that attract CD4 and CD8 T cells. T cell infiltration into the tumor slows down cancer progression and prolongs patient survival.