Macrophages and cancer

Pat W. Whitworth, Charles C. Pak, Joseph Esgro, Eugenie S. Kleinerman and Isaiah J. Fidler
Department of Cell Biology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

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Abstract

The uncontrolled growth of metastases resistant to conventional therapeutic modalities is a major cause of death from cancer. Data from our laboratory and others indicate that metastases arise from the nonrandom spread of specialized malignant cells that preexist within a primary neoplasm. These metastases can be clonal in their origin, and different metastases can originate from different progenitor cells. In addition, metastatic cells can exhibit an increased rate of spontaneous mutation compared with benign nonmetastatic cells. These data provide an explanation for the clinical observation that multiple metastases can exhibit different sensitivities to the same therapeutic modalities. These findings suggest that the successful therapy of disseminated metastases will have to circumvent the problems of neoplastic heterogeneity and the development of resistance.

Appropriately activated macrophages can fulfill these demanding criteria. Macrophages can be activated to become tumoricidal by interaction with phospholipid vesicles (liposomes) containing immunomodulators. Tumoricidal macrophages can recognize and destroy neoplastic cells in vitro and in vivo, leaving non-neoplastic cells uninjured. Although the exact mechanism(s) by which macrophages discriminate between tumorigenic and normal cells is unknown, it is independent of tumor cell characteristics such as immunogenicity, metastatic potential, and sensitivity to cytotoxic drugs. Moreover, macrophage destruction of tumor cells apparently is not associated with the development of tumor cell resistance.

Macrophages are found in association with malignant tumors in a definable pattern, suggesting that the most direct way to achieve macrophage-mediated tumor regression is in situ macrophage activation. Intravenously administered liposomes are cleared from the circulation by phagocytic cells, including macrophages, so when liposomes containing immunomodulators are endocytosed, cytotoxic macrophages are generated in situ. The administration of such liposomes in certain protocols has been shown to bring about eradication of cancer metastases.

Macrophage destruction of metastases in vivo is significant, provided that the total tumor burden at the start of treatment is minimal. For this reason, we have been investigating various methods to achieve maximal cytoreduction in metastases by modalities such as chemotherapy or radiotherapy prior to macrophage-directed therapy. It is important to note that even the destruction of 99.9% of cells in a metastasis measuring 1 cm² would leave $10^6$ cells to proliferate and kill the host. The ability of tumoricidal macrophages to distinguish neoplastic from bystander nonneoplastic cells presents an attractive possibility for treatment of the few tumor cells which escape destruction by conventional treatments.

Macrophage-directed therapy has been studied in several human protocols, yielding important biological information about the use of liposome-encapsulated macrophage activators in cancer patients. Currently, Phase II and Phase IIB protocols are being conducted based on the results from Phase I trials.
Introduction

Cancer and metastasis

The most devastating aspect of cancer is the spread of tumor cells from the primary neoplasm to distant organs, resulting in the development of secondary tumors, i.e., metastases. The process of cancer metastasis involves a series of discrete steps. First, cells must escape from the primary tumor, then disseminate to distant sites, arrest in the microcirculation of distant organs, extravasate into and infiltrate the stroma of those organs, and finally survive and grow into new tumor foci. The outcome of this process depends on both host factors and tumor cell properties. Thus, specific consequences of these host-tumor interactions vary among different tumor systems [1-3].

Despite advances in our understanding of cancer biology, in general patient care, in surgical techniques, and in adjuvant therapy the majority of deaths from cancer are still caused by the growth of metastases that are resistant to conventional therapies. There are several reasons for this lack of success in the treatment of metastasis. First, efforts to prevent the establishment of metastases are not often clinically relevant because, in the majority of patients with metastases, metastasis has occurred by the time of diagnosis of the primary malignant neoplasm [3]. Second, the anatomical location and number of metastases often preclude response to the dose of a therapeutic agent that can be delivered to the lesion without producing severe toxicity in the host. Third, the heterogeneous nature of malignant neoplasms, manifested by the continuous emergence of new variant tumor cells, results in the development of cell subpopulations resistant to the therapeutic agents that are initially effective [3].

By the time of diagnosis, and certainly in clinically advanced lesions, malignant tumors contain multiple cell populations that exhibit a wide range of biological heterogeneity in, for example, cell surface features, antigenicity, immunogenicity, growth rate, karyotype, drug sensitivity, and the ability to invade and metastasize [2-5].

Biological diversity is equally prominent among cells in metastatic lesions [3]. Recent data derived from a number of tumors of different histologies help explain these findings. The process of metastasis is selective [3], and metastases are produced by the nonrandom dissemination and establishment of specialized subpopulations of cells that are present in the primary tumor [6]. Although metastases can be clonal in origin, different metastases, even those within the same organ, can originate from different progenitor cells [7-10], and a metastasis can originate from the proliferation of a single metastatic cell [11]. Collectively, these findings provide an explanation for the clinical observation that different metastases often exhibit different sensitivities to immunotherapy, chemotherapy, and radiotherapy [3, 4]. The problem of neoplastic heterogeneity is further complicated by the fact that, in general, metastatic cells are genetically unstable and rapidly develop resistance to chemotherapy [12]. For all these reasons, the successful treatment of metastatic disease will require the development of new strategies with a spectrum of activity that overcomes the existing cellular diversity of neoplasms. In particular, modalities are required to overcome the development of tumor cells resistant to conventional therapy.

Indeed, the extensive cellular diversity of neoplasms suggests that the successful treatment of metastases requires the total destruction of all cancer cells. This concept is illustrated in Fig. 1. By the time a neoplastic lesion is diagnosed, the tumor could measure 1 cm$^3$ (or greater), and thus contain one billion cells. The destruction of 99.9% of the cells is insufficient to produce a cure, since it leaves one million cells to proliferate and generate treatment-resistant variant cells.

Thus, the challenge to the basic researcher and clinical oncologist is clear. New approaches for eradicating the tumor cells that resist conventional therapies must be developed. Such approaches have to circumvent the problem of neoplastic heterogeneity and the emergence of treatment-resistant tumor cells [13]. During the last few years, studies from our laboratory and many others have suggested that a biological approach to eliminating the few fatal tumor cells that resist or escape conventional therapies can be accomplished by the systemic activation of macrophages.