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T Lymphocytes Restrain Spontaneous Metastases in Permanent Dormancy

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Abstract

Tumor dormancy is a clinical phenomenon related to immune equilibrium during cancer immunoediting. The mechanisms involved in dormant metastases are poorly understood due to the lack of preclinical models. Here, we present a nontransgenic mouse model in which spontaneous metastases remain in permanent immunomediated dormancy with no additional antitumor treatment. After the injection of a GR9-B11 mouse fibrosarcoma clone into syngeneic BALB/c mice, all animals remained free of spontaneous metastases at the experimental endpoints (3–8 months) but also as long as 24 months after tumor cell injection. Strikingly, when tumor-bearing mice were immunodepleted of T lymphocytes or asialo GM1-positive cells, the restraint on dormant disseminated metastatic cells was relieved and lung metastases progressed. Immunostimulation was documented at both local and systemic levels, with results supporting the evidence that the immune system was able to restrain spontaneous metastases in permanent dormancy. Notably, the GR9-B11 tumor clone did not express MHC class I molecules on the cell surface, yet all metastases in immunodepleted mice were MHC class I–positive. This model system may be valuable for more in-depth analyses of metastatic dormancy, offering new opportunities for immunotherapeutic management of metastatic disease. *Cancer Res; 74(7); 1958–68. ©2014 AACR.*

Introduction

The initiation and progression of cancer in an immunocompetent host involve numerous interactions between tumor cells and the immune system. The immune response exercises selective pressure against tumor cells, eliminating the more immunogenic phenotypes. This constant interaction between the immune system and cancer cells may ultimately result in the selection of less immunogenic "cancer-escape" variants that are able to survive and progress in the host (1, 2). The diverse escape mechanisms developed by cancer cells to evade the immune response (3–6) include the loss of surface expression of MHC class I molecules (7–9). This loss may make the tumor cells invisible to T lymphocytes, allowing them to enter an "immunoblindness" stage (10).

It is feasible that some cancer cells neither progress nor are destroyed by immune system during this selective process, remaining in a dormant stage and reaching equilibrium with the host tumor microenvironment (11–13). Cancer dormancy has been observed in humans (14, 15), and several experimental studies have reported an immunomediated control of primary tumor cells in dormancy (16–20). There is considerable evidence of metastasis relapse in human cancer patients after long periods of remission, when disseminated metastatic cells can persist for years or even decades as minimal residual disease (21, 22). Other clinical examples related to cancer immune control include tumors that arise after immunosuppressive treatments (23, 24) and cases of transplanted organs carrying an undetectable tumor that grows after immunosuppressive treatment of the patient (25–27). These clinical phenomena support the existence of a state of equilibrium between the host and the cancer cells. The fact that immunosuppression can disturb this equilibrium and activate dormant cancer cells strongly suggests the existence of an immunomediated state of dormancy in these cases.

The mechanisms involved in cancer dormancy remain largely unknown, due to difficulties in isolating dormant human metastatic cells and constructing preclinical models of dormant metastases. Here, we presented a novel nontransgenic preclinical mouse model of permanent immunomediated metastatic dormancy. We have used an extensively studied fibrosarcoma mouse model (GR9) developed in our laboratory composed of several tumor clones with different MHC class I expression patterns and spontaneous metastatic capacities (28). Thus, the metastatic capacity is elevated in the clones with high MHC class I expression and reduced in those with low MHC class I expression (29). We show that an MHC-I-negative GR9-B11 tumor cell clone did not generate spontaneous lung metastasis in immunocompetent mice, which

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