The Role of Tumor-Infiltrating Lymphocytes in Development, Progression, and Prognosis of Non–Small Cell Lung Cancer

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ABSTRACT

A malignant tumor is not merely an accumulation of neoplastic cells, but constitutes a microenvironment containing endothelial cells, fibroblasts, structural components, and infiltrating immune cells that impact tumor development, invasion, metastasis, and outcome. Hence, the evolution of cancers reflects intricate cellular and molecular interactions between tumor cells and constituents of the tumor microenvironment. Recent studies have shed new light on this complex interaction between tumor and host immune cells and the resulting immune response. The composition of the immune microenvironment differs across patients as well as in cancers of the same type, including various populations of T cells, B cells, dendritic cells, natural killer cells, myeloid-derived suppressor cells, neutrophils, and macrophages. The type, density, location, and organization of immune cells within solid tumors define the immune contexture, which has proved to be a major determinant of tumor characteristics and patient outcome. Lung cancer consists mostly of non–small cell lung cancer (85%); it is our most deadly malignant disease, with the 5-year survival rate being merely 15%. This review focuses on the immune contexture; the tumor-suppressing roles of tumor-infiltrating lymphocytes; and the relevance of this immune contexture for cancer diagnostics, prognostication, and treatment allocation, with an emphasis on non–small cell lung cancer.

Keywords: Tumor microenvironment; TILs; Prognosis; Immune context; Immunoscore; NSCLC

Introduction

Until recently, the principal focus in cancer research was the malignant cell, with relative neglect of the tumor's microenvironment represented by endothelial, stromal, and immune cells; components of the extracellular matrix; and an abundance of mediators.[1] Already 50 years ago, while still discussing whether the immune system had positive, negative, or no effects on tumor development, Burnet and Thomas proposed the hypothesis of immunological surveillance, in which the immune system acts as a sentinel by detecting and eliminating nascent transformed cells and thereby protecting against cancer development.[2,3] This hypothesis

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was, however, abandoned shortly afterwards owing to the absence of strong experimental evidence.

During the past 15 years, the groundbreaking adaptive immunity studies in mice by Schreiber et al. have clearly proved the existence of cancer immunosurveillance.[4–7] This concept has been further refined into cancer immunoediting, incorporating a broader view of tumor–immune system interaction.[8] During this progress, we have witnessed a radical change of view on malignancy, from it being an autonomous cellular disease comprising six biological capabilities[9] to it being a regulated disease involving the immune components of its microenvironment.[10] Through interactions with tumor cells, immune cells will induce tumor fates according to the three E phases (elimination, equilibrium, or escape) by activation of innate and adaptive immune responses.[6] The work by Schreiber et al. definitely altered the field of cancer immunology, and "evading immune destruction" was added as an emerging hallmark in the revision of "The Hallmarks of Cancer."[10]

Early clinical studies revealed that tumor-infiltrating lymphocytes (TILs) had a major impact on the clinical course of several cancers.[11–18] More recently, Fridman et al. reviewed the effect of T cells on the clinical outcome of a variety of solid cancers and found that a strong infiltration of TILs was associated with a positive clinical outcome in several cancers, including melanoma as well as head and neck, breast, bladder, urothelial, ovarian, colorectal, renal, prostatic, and lung cancer.[19] More specifically, the most consistent positive prognostic impacts were demonstrated for T cells, especially cytotoxic T cells, memory T cells, and T helper cells 1.[19] These data not only elucidate the relationship between immunity and cancer but will also have consequences for the management of malignant disease. In colorectal and lung cancer, it has more recently been established that TILs can differentiate prognosis within each tumor, node, and metastasis (TNM) stage,[20,21] rendering type and density of TILs to be powerful prognostic factors complementing or even outperforming pathological criteria alone.

In 2011, Goldstraw et al. declared that the TNM classification had stood the test of time and remained the most powerful prognostic instrument for lung cancer.[22] In line with the rapidly increasing documentation of the profound prognostic impact by TILs in malignant tumors, including non–small cell lung cancer (NSCLC), one may argue that this perception needs to be revised.

Cancer Immunosurveillance, Immunoediting, and Immune Contexture

The immune infiltrate, in lung cancers as well as in other malignancies, has been shown to comprise adaptive and innate immune cells.[19,23,24] Besides, immune infiltrates are heterogeneous across both tumor types and patients with cancer.[19] All immune cell types may be present in a tumor, and they include macrophages, neutrophil granulocytes, dendritic cells, mast cells, natural killer (NK) cells, naive and memory lymphocytes, B cells, and effector T cells (T helper cells 1, 2, and 17; regulatory T [Treg] cells; T follicular helper cells; and cytotoxic T cells). These may be localized in the tumor core, invasive margin, or adjacent tumor stroma. The immune cell type, density, and location, as well as the functional orientation of involved immune cell populations constitute the *immune contexture*, whereas chemokines and cytokines are involved in shaping it.[25]

Observational studies linked to clinical outcome data have suggested both the existence and relevance of the immune surveillance phenomenon in humans, which was characterized earlier by Schreiber et al.[7] Through this dynamic process, the immune system not only protects against cancer development but also appears to shape the character of emerging tumors according to the concept of immunoediting.[26] Herein, we will convey how the immune system plays a dual role in cancer progression as it can not only suppress tumor growth by eliminating cancer cells but also promote tumor growth by selecting cancer cells that can evade surveillance.

The three phases of immunoediting are elimination, equilibrium, and escape (Fig. 1).[6,8,27] In the *elimination* phase, innate and adaptive cells of a competent immune system can together detect and destroy early tumors before they become clinically apparent. Such tumor cells are immunogenic, expressing antigens that differentiate them from nontransformed cells, and the balance is toward antitumor immunity. Cancer cells that survive the elimination phase enter the *equilibrium* phase, in which the immune system holds the tumor in a state of dormancy. Some tumor cells undergo genetic/epigenetic changes, and owing to constant immune pressure, new evolving tumor cells can resist immune recognition. In this phase there is a balance between antitumor and tumor-promoting cytokines. During the *escape* phase, tumor cells can induce an immunosuppressive state through production of cytokines and growth factors, as well as by recruiting immunosuppressive cells, leading to an impairment of effector T cells. Next, tumor cells evade immune recognition and the immune system fails to restrict tumor growth, eventually causing clinical disease. These tumor cells generally express molecules with increased resistance, survival, immunosuppression, and angiogenesis, which again induce the generation of immunosuppressive cells (e.g., Treg cells and myeloid-derived suppressor cells) and cytokines. Progression during the escape phase explains the paradoxical observation of tumor development in immunocompetent