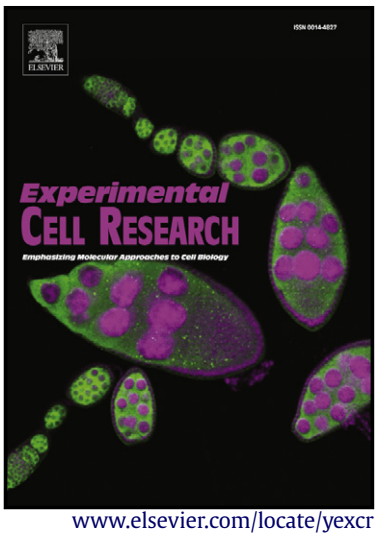

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An inflammatory vicious cycle: fibroblasts and immune cell recruitment in cancer

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Abstract

Cancer-associated fibroblasts (CAFs) have been established as a key component of the crosstalk between tumor cells and their microenvironment. The ability of CAFs to orchestrate tumor-promoting inflammation is central to their role in facilitating tumor growth, invasion, and metastasis. Here we review pathways by which CAFs and their soluble mediators provide multiple complex signals that modulate the recruitment, functional activation status, and retention of immune cells in the tumor microenvironment.

Keywords:
Cancer-associated fibroblasts; inflammation; cancer; microenvironment

Introduction

Inflammation is now accepted as an enabling characteristic of cancer [1, 2]. Inflammatory mediators such as chemokines and cytokines as well as cells of the innate and adaptive immune systems are important constituents of the microenvironment in virtually all solid tumors, even those that are not etiologically related to inflammation [3]. Although the specific inflammatory molecular circuits and cellular components may be tumor type specific, the chronic recruitment and presence of activated leukocytes in tumors is a hallmark of the tumorigenic process and a predictor of aggressive disease [4]. Immune cells facilitate tumor growth and progression by regulating angiogenesis, invasion and metastasis [3, 5-8]. More recently, leukocytes were also implicated in regulating the response of tumors to cytotoxic therapy [9-11].

There has been extensive research in recent years focusing on the recruitment of various immune cells to the microenvironments of primary tumors, as well as to sites of metastases. Tumor cells were shown to secrete chemokines and cytokines that facilitate the recruitment and functional activation status of myeloid cells as well as lymphocytes that facilitate tumor growth and metastasis [5, 8]. Macrophages and T lymphocytes were also implicated in mutually affecting the recruitment and reprogramming of each other towards a tumor-promoting phenotype [12-14]. However, the role of Cancer-Associated Fibroblasts (CAFs) as novel key players in mediating recruitment of immune cells into various cancer types is only recently emerging.

CAFs are a heterogeneous population of fibroblastic cells that constitute the most prominent stromal cell type in the microenvironment of many solid tumors, in particular