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Tumor regulation of the tissue environment in the liver

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ABSTRACT

The tumor microenvironment (TME) in the liver plays an important role in primary and metastatic liver tumor formation and tumor growth promotion. Cellular and non-cellular components of the TME significantly influence tumor development, growth, metastatic spread, anti-tumor immunity and response to tumor therapy. The cellular components of the TME in the liver not only consist of infiltrating immune cells, but also of liver-resident cells such as liver sinusoidal endothelial cells (LSEC) and hepatic stellate cells (HSC), which promote tumor growth by negatively regulating tumor-associated immune responses. In this review, we characterize cells of the TME with pro- and anti-tumor function in primary and metastatic liver tumors. Furthermore, we summarize mechanisms that permit growth of hepatic tumors despite the occurrence of spontaneous anti-tumor immune responses and how novel therapeutic approaches targeting the TME could unleash tumor-specific immune responses to improve survival of liver cancer patients.

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Contents

1. Introduction

The TME of solid tumors has gained enormous attention in recent years, as it has become clear that its cellular and non-cellular components significantly influence tumor development and growth, metastatic spread, anti-tumor immunity and response to tumor therapy (Hanahan & Weinberg, 2011; Joyce & Fearon, 2015). The cellular component of the TME can be subdivided into immune cells and non-immune cells. Lymphocytes and myeloid cells from the immune cell compartment and endothelial cells, pericytes and fibroblast form the non-immune cell compartment of the TME. Importantly, the liver contains specialized endothelial cells and specialized fibroblast, namely LSEC and HSC, respectively, that perform immune functions (Jenne & Kubes, 2013; Thomson & Knolle, 2010). All of these aforementioned cell types can influence the tumor and in turn can be influenced by the tumor through a variety of mechanisms. Thus, understanding the tumor-promoting, therapy-inhibiting mechanisms of the TME is instrumental for the design of successful treatment approaches.

In the liver, it is important to distinguish between the TME of primary hepatic tumors, commonly residing in inflamed liver tissue, and the TME of liver metastases of non-hepatic tumors, residing in otherwise healthy liver tissue. Hepatic immune cells play an important role in primary liver cancer formation and growth and also in 'preparing' the liver for metastatic seeding of tumors from different primary sites. In patients

Abbreviations: CTL, cytotoxic T cells; HCC, hepatocellular carcinomas; HSC, hepatic stellate cells; LSEC, liver sinusoidal endothelial cells; MDSC, myeloid-derived suppressor cells; NASH, non-alcoholic steatohepatitis; NK cells, Natural Killer cells; TAM, tumor-associated macrophages; TME, tumor microenvironment; T reg, regulatory T cells.

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with liver metastasis but without underlying liver disease, the primary tumor, e.g. colon carcinoma, recruits myeloid cells to the liver to enable metastatic seeding of colon cancer cells (Zhao et al., 2013). These myeloid cells also induce down-regulation of angiopoietin-like 7 protein in cancer cells to promote angiogenesis and metastasis formation (Lim et al., 2015). Moreover, hepatic resident non-immune cells can also support metastasis development in the liver. Because of the liver's unique anatomical location and metabolic functions in the human body, the resident immune and non-immune cells of the liver are endowed with distinctive functional properties (Thomson & Knolle, 2010). For example, LSEC sample the blood, which contains nutrients and microbial antigens from the gut, and induce T cell tolerance to antigens to which no preexisting immunity exists (Schurich et al., 2009). However, the same mechanism also leads to hepatic tolerance towards tumor-associated antigens and enables metastatic spread into the liver (Arteta et al., 2010; Hochst et al., 2012), illustrating one non-immune cell-mediated mechanism of tumor immune escape that is unique to the liver.

The TME of hepatocellular carcinomas (HCC), the most frequent primary liver cancer, is even more complex, because HCC usually develop in chronically inflamed livers. Indeed, chronic liver inflammation, induced by non-alcoholic steatohepatitis (NASH) or viral hepatitis, can progress to liver cirrhosis and eventually to carcinomas (El-Serag & Rudolph, 2007). Therefore, both the tumor and the underlying chronic liver inflammation shape the TME of HCC. This is particularly important for the function of myeloid cells. Macrophages, for example, can prevent outgrowth of HCC in otherwise healthy livers by clearing precancerous hepatocytes (Kang et al., 2011), but they can also initiate HCC development in inflamed livers (Lanaya et al., 2014). The chronic inflammation that drives liver cancer formation is also responsible for the regular occurrence of tumor neoantigens, which can trigger an anti-tumor T cell immune response (Schumacher & Schreiber, 2015). Consequently, tumor antigen-specific T cells can infiltrate HCC and several HCC-associated epitomes that are recognized by the infiltrating T cells have been identified (Flecken et al., 2014; Mizukoshi et al., 2011). Despite the recognition of and infiltration into the tumor by the immune system, HCC remains a cancer with a high mortality and poor 5-year survival (Njei, Rotman, Ditah, & Lim, 2015). This suggests that potent tumor-associated immunosuppressive mechanisms are in place to escape the immune response in patients with HCC. Indeed, myeloid-derived suppressor cells (MDSC) and regulatory T cells (T reg) are commonly found immune suppressive cells in HCC (Fu et al., 2007; Hoechst et al., 2008). Together, these findings underscore the significance of immune cells in primary and metastatic tumor development and tumor control in the liver (Fig. 1).

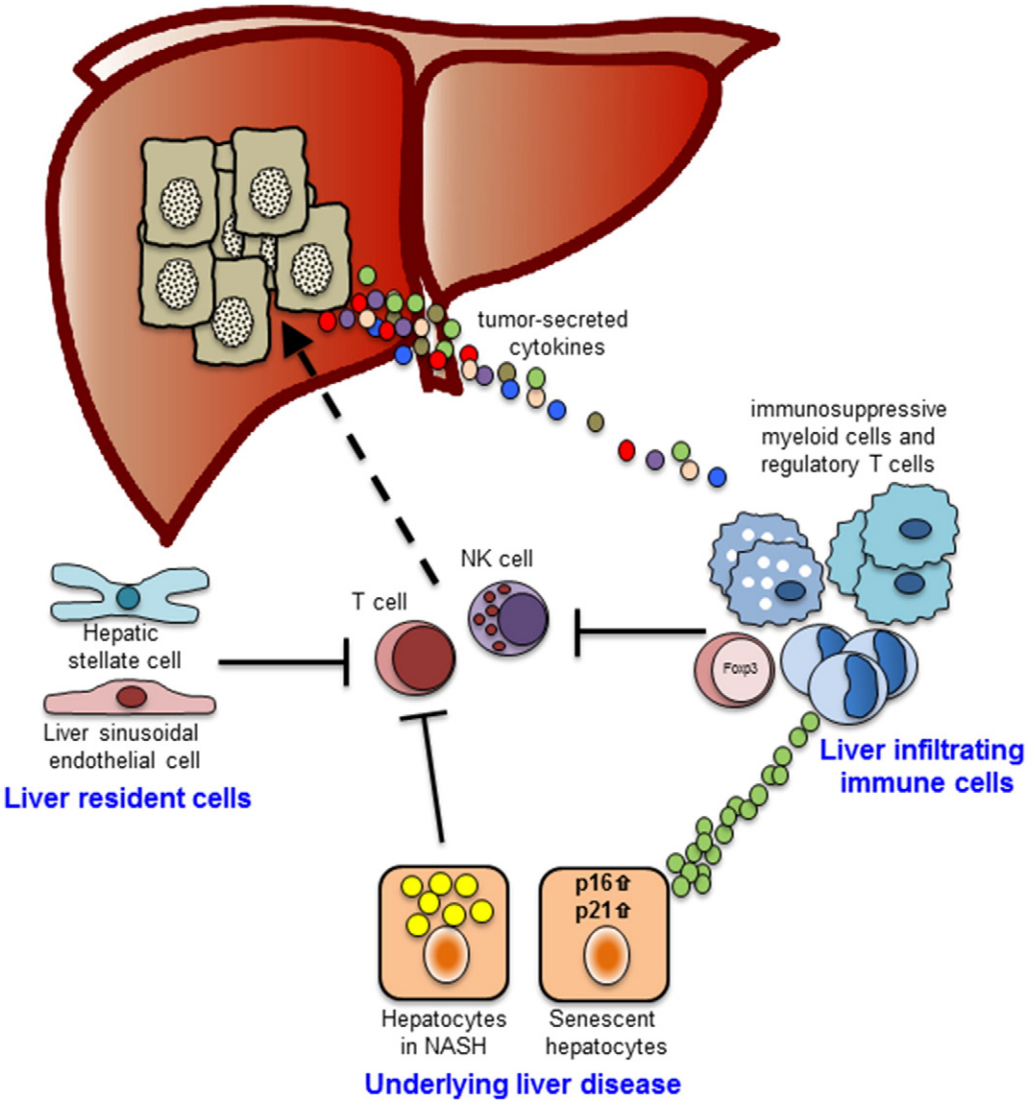

Fig. 1. Components of the tumor microenvironment restraining anti-tumor immune cells. Following activation, T cells and NK cells target tumors for tumor cell killing. However, liver resident cells and/or liver infiltrating immune cells such as immunosuppressive myeloid cells or regulatory T cells inhibit their anti-tumor function. Furthermore, the underlying liver disease also negatively regulates T cell and NK cell function either directly by inducing of CD4 T cell death or indirectly by recruiting immunosuppressive myeloid cells.