Immunosuppressive mechanism of hepatocellular carcinoma

肝細胞癌的免疫抑制機制

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Research Background

Liver cancer, of which hepatocellular carcinoma (HCC) comprise the majority, is the 3rd leading cause of cancer death worldwide. 80% of global cases occur in Asia, with 55% of new diagnoses occurring in China. Over 70% of patients present with advanced disease that renders them unsuitable for transplant, surgical resection or ablation options. For these patients there remains a paucity of approved therapeutic options. Sorafenib treatment offers a 3-month increase in median survival for late-stage HCC, which is around one year. Liver cirrhosis precludes the potential use of many cytotoxic drugs, making the development of prospective chemotherapy relatively difficult. There is clearly a dire need for new therapeutic options for HCC for all stages of the disease.

Cancer immunotherapy that elicit an antitumor T cell response via the activation of dendritic cells (DCs) is a promising strategy. A therapeutic DC vaccine has been developed for prostate cancer. However, its efficacy is quite modest, likely due to the well-documented immunosuppressive effects of the tumor microenvironment (TME) on DC activity. The precise molecular mechanisms and effectors that mediate TME repression of DC activity are unclear.

Of the different DC subtypes found in the TME, plasmacytoid dendritic cells (pDCs) are found to be preferentially enriched in many malignancies, including lung cancer, ovarian cancer, and indeed, HCC. In HCC, pDCs have been shown to remain in an immature state, which correlates with increased levels of immunosuppressive regulatory T cells (Tregs) and worse prognoses. The immature phenotype of pDC observed within HCC TME suggests that pDC dysfunction may be the culprit that drives immunosuppression in the HCC TME.

While pDC infiltration in the TME often correlates with worse prognoses, pDC-driven antitumor immunity has been clearly demonstrated in multiple studies. Injection of activated pDCs loaded with tumor-associated antigen (TAA) peptides led to favorable T cell response in melanoma patients. In a murine mammary tumor model, intratumoral

administration of a toll-like receptor 7 (TLR7) agonist activated pDCs within the TME and had potent antitumor effects. In a melanoma mouse model, TLR-stimulated pDCs mediate tumor killing. These lines of evidence strongly support that pDCs are effective antitumor agents, and when activated appropriately, can serve as potent cancer immunotherapy. Stimulating/reactivating tumor-associated pDC is therefore a promising therapeutic option.

In this study, we will first use in vitro systems to identify the immunosuppressive factors in the HCC tumor microenvironment (TME) to establish the molecular mechanisms of immune evasion. While many studies have demonstrated the immunosuppressive effects of various cytokines and microRNAs (miRNAs) in the TME, different tumor types have been shown to employ different immune evasion strategies. To date, no HCC specific immunosuppressive factor has been defined. Results from this study will discover potential therapeutic targets for HCC. In addition, this work will elucidate how immunosuppressive factors circumvent immune cell activation. Overall, the results will be directly applicable to designing novel immunotherapeutic strategies for HCC. Because pDC suppression has been implicated in various tumors, results from this study can potentially be applicable to other malignancies as well.

Research Objectives

Aim 1: Determine the effects of HCC TME on pDC function: pDC activity will be assessed after long term coculture with HCC secreted products.

Aim 2: Identify the factors that modulates pDC functions: secreted HCC protein or RNA effectors that mediate pDC suppression will be identified