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Research review

The prognostic value of liver tumor T cell infiltrates

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ARTICLE INFO

Article history:
Received 7 April 2014
Received in revised form
18 May 2014
Accepted 2 June 2014
Available online 7 June 2014

Keywords:
Tumor infiltrating lymphocytes
Immunotherapy
Programmed death-1
Liver tumors
T cells

ABSTRACT

Tumor infiltrating lymphocytes (TIL) have been demonstrated to predict oncologic outcomes following resection of primary intrahepatic neoplasms and metastatic liver tumors. Despite strong immunosuppressive factors within the intrahepatic space, TIL are frequently demonstrated in liver tumors. The presence of TIL within liver tumors provides evidence of a host immune response that may be protective, but often is rendered ineffective by tumor induced immune dysfunction. In this review, we discuss techniques involved in studying TIL and subsets of TIL commonly identified. We emphasize the unique nature of the intrahepatic milieu that promotes immunosuppression, and how liver TIL and TIL ratios can be used as indicators of prognosis. Several types of primary and metastatic liver tumors are considered to highlight the similarities and important differences in TIL responses, which likely reflect how intrahepatic immunity is influenced by tumor biology. The studies we discuss indicate that tumor infiltration by suppressor cells and expression of immunoinhibitory molecules by TIL limits the anti-tumor immune function of effector T cells. Most patients fail to mount an adequate immune response to liver tumors, which provides compelling rationale for clinical study of immunotherapy for intrahepatic neoplasms.

1. Introduction

Tumor infiltrating lymphocytes (TIL) are thought to represent a specific host response to tumor antigens and may be used for therapeutic purposes following isolation, or studied for prognostic information [1,2]. A growing body of literature supports the biologic relevance of TIL as predictors of outcome for primary and metastatic tumors [3,4]. TIL have been demonstrated to predict outcomes in a wide variety of solid tumors [1,5], with the magnitude of this effect being dependent on tumor site and disease stage [6]. We previously reviewed solid tumor immunotherapy, including the therapeutic use of TIL [7]. Although the present review focuses on the prognostic importance of TIL in liver tumors, it is important to emphasize that TIL, along with other forms of adoptive cell therapy, will play an increasingly important role in immunotherapy.

TIL have been demonstrated to predict survival and recurrence following resection of both primary and metastatic liver tumors [3,4,8]. TIL are frequently demonstrated in liver tumors despite strong immunosuppressive factors within the

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0022-4804/$ – see front matter
http://dx.doi.org/10.1016/j.jss.2014.06.001

intrahepatic space. The presence of TIL within liver tumors provides evidence of a host immune response that may provide protection against disease progression, but often is rendered ineffective by tumor-induced immune dysfunction. Interest in studying TIL within liver tumors is predicated on the desire to understand the immune response to intrahepatic neoplasia, in addition to the value of TIL as biomarkers to predict outcome. In this review, we discuss techniques involved in assessing TIL, subsets of TIL commonly studied, the unique nature of the intrahepatic milieu that promotes immunosuppression, and how liver TIL can be used as indicators of prognosis. Several types of primary and metastatic liver tumors are considered to highlight the similarities and important differences in TIL responses, which likely reflect how intrahepatic immunity is influenced by tumor biology.

1.1. *The immunosuppressive intrahepatic space*

At baseline, the liver has a strong tendency to promote tolerance to intrahepatic antigens [9,10]. Non-parenchymal cells in the liver, including sinusoidal endothelial cells [11], dendritic cells (DC) [12], and natural killer [13] cells have been demonstrated to contribute to the tolerogenic intrahepatic milieu. The immunosuppressive nature of liver T cells has been described as well [11,12,14]. The suppressive influence of liver non-parenchymal cells likely works in concert with tumor-induced immunosuppression to prevent eradication of intrahepatic tumors by liver TIL.

Tumors may downregulate expression of MHC class I molecules, thereby preventing effector T cells from recognizing tumor antigens. Moreover, tumors may secrete molecules that promote the influx of suppressive immune cells in addition to augmenting suppressor cell function [15]. As such, assessment of liver TIL provides important insight into the biology of the underlying neoplastic process. More importantly, a deeper understanding of the nature and functional limitations of liver TIL may reveal new therapeutic opportunities through manipulation of effector and suppressor TIL subsets.

1.2. *TIL subsets*

It is important to discriminate among different liver TIL subtypes, as they have markedly different functions within the tumor microenvironment. Because T lymphocytes are primarily responsible for antigen-specific immune responses and they typically comprise the largest proportion of TIL, much of the TIL literature is devoted to the study of T cell subsets. In a recent meta-analysis, Gooden *et al.* [6] demonstrated that the extent of tumor infiltration by T cells was a significant correlate of overall survival. TIL other than T cells, including B cells and NK cells, have been studied as well but will not be addressed in detail in this review. Our understanding of the biologic implications of non-T cell TIL is less developed at this time.

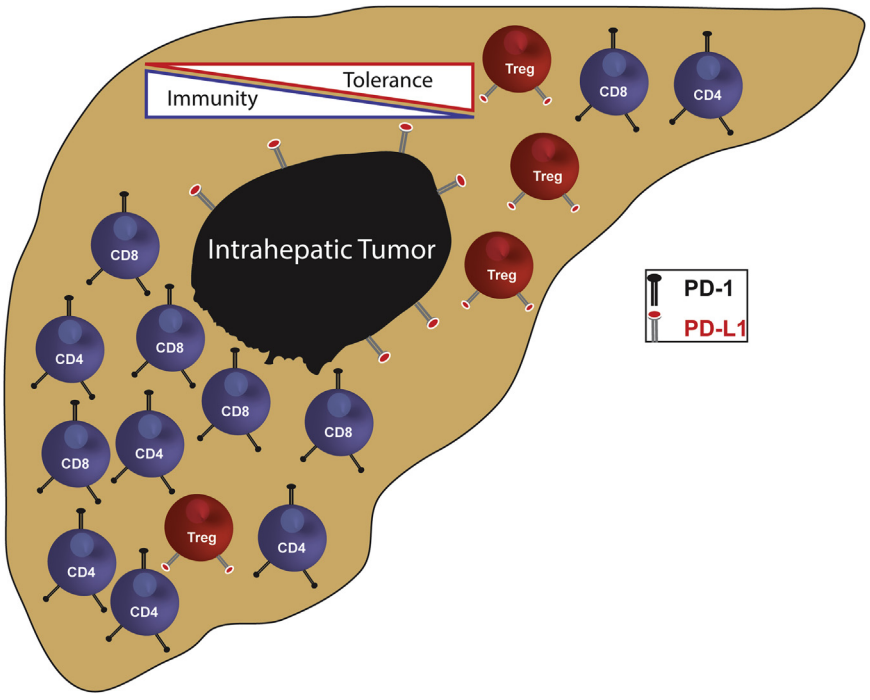

Figure – Liver TIL. Left: a favorable T cell infiltrate is depicted approaching an intrahepatic tumor. An abundance of CD4 T cells is present to support tumor cell killing by high density of cytotoxic CD8 T cells. Few regulatory T cells (Treg) are present, providing a favorable ratio of effector to suppressor T cells. Right: an unfavorable T cell infiltrate is thwarting anti-tumor immunity. A high ratio of suppressive Treg to effector CD4 and CD8 T cells is promoting tolerance and will hinder tumor clearance. PDL-1 on the surface of Treg and the tumor cells will engage PD-1 on CD4 and CD8 T cells to suppress anti-tumor immune activity.