Challenge in cancer therapy with VAP-1 inhibition strategy: possible interference of this type of intervention within protection from autoimmunity: Hypothesis

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\textbf{A B S T R A C T}

Vascular adhesion protein-1 (VAP-1) is an endothelial cell surface-expressed oxidase involved in leukocyte traffic. The adhesive function, and therefore leukocyte infiltration to different tissues, can be blocked by anti-VAP-1 antibodies as well as small molecule VAP-1 inhibitors. Several papers have been published on the effect of VAP-1 blockade on both leukocyte accumulation into tumors and neoangiogenesis. Additionally, myeloid derived suppressor cells (MDSCs) have been identified as immunosuppressive cells associated with tumor expansion. Moreover, some of them (such as CD11b\textsuperscript{+} myeloid cells) appear to be intrinsically suppressive and may have a key role in maintaining immune homeostasis and protection from autoimmunity. Since VAP-1 supports leukocyte emigration (including MDSCs) to normal tissues and sites of inflammation like tumor tissue, its inhibition has been suggested as potential cancer immunotherapy intervention. Moreover, since these types of suppressive cells use VAP-1 mediated strategy for their adhesion and infiltration, it is hypothesized that VAP-1 inhibition may lead to partial loss of suppressive function on immune system and therefore induce the development of autoimmune diseases like relapsing-remitting (experimental) autoimmune encephalomyelitis.

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Introduction

Immune responses directed against pathogens and self-modified antigens (Ags) occur following the initial step of specific Ag recognition and the transmission of activating signals mediated by the pre-T cell receptor (TCR) complex [1-3]. Leukocyte trafficking from blood to tissues is not only a prerequisite for mounting normal immune responses against microbes but also needed for immunosurveillance against malignantly transformed cells [4]. Also, various subsets of hematopoietic cells and/or derived factors are involved in these immunoregulatory processes to prevent autoimmunity [5, 6].

Myeloid derived suppressor cells (MDSCs), which show heterogeneous phenotypes including immature granulocytes, monocytes/macrophages (Mφ), dendritic cells (DCs) and early myeloid progenitors, have been originally identified as immunosuppressive cells in association with tumor expansion [7]. These cells have been reported to express CD11b (integrin αM subunit) and GR-1 (a myeloid differentiation antigen with known Ly6G and Ly6C components) in mouse models [8-13]. In tumor microenvironment, MDSCs inhibit T cell activation via arginase (ARG)-1 and nitric oxide activation, resulting in tumor growth [11]. Adversely, MDSCs play a critical role in other conditions such as immunoregulatory processes to prevent autoimmunity disorders [14-18]. According to Slaney et al. [19], the loss of suppressive function by blood CD11b+ Ly6G cells following induction of experimental autoimmune encephalomyelitis (EAE) provides evidence to suggest that these cells may have a part in maintaining immune tolerance and protection from autoimmunity.

Normally, leukocytes leave the blood using a multistep extravasation cascade involving many activation and adhesion molecules both on the leukocyte surface and on the endothelial lining [4]. Endothelial adhesion molecules are needed for leukocyte extravasations into normal tissues as well as into tumors [20]. Among them, a cell surface expressed amine oxidase vascular adhesion protein-1 (VAP-1) supports leukocyte emigration into the sites of inflammation [21]. VAP-1 is expressed in normal tissues in the vein endothelial cells in the pericytes and smooth muscle cells, and also in adipocytes [22, 23]. In these cells, it is mainly present in intracellular vesicles, which then translocate the molecule onto the luminal surface upon certain inflammatory stimuli [24]. Leukocyte migration into tumors can have two opposite outcomes in tumor progression [1]. Extravasation of cytotoxic leukocytes, such as CD8+ T cells and NK cells, can lead to enhanced antitumor immune responses, which may limit tumor growth [2]. Infiltration of the immune-suppressing leukocyte types, such as regulatory T cells or type 2 macrophages, into the malignancy leads to defective immune responses. In fact, tumor cells themselves actively secrete molecules that lead to the recruitment of these immune-suppressing leukocyte types and are able to use misguided leukocyte traffic as one way of tumor escape from the immune system [25, 26]. Leukocytes normally use a multistep adhesion cascade to enter tissues. Several endothelial adhesion molecules engaging their cognate leukocyte ligands play an important role in this process. Among them, VAP-1 supports recruitment of Gr-1+ CD11b+ myeloid cells into tumors [25]. It has been reported [25, 26] that both anti-VAP-1 antibodies and VAP-1 inhibitors reduce the number of leukocytes in the tumors, but they target partially different leukocyte subpopulations. Anti-VAP-1 mAbs also selectively inhibited infiltration of CD8+ lymphocytes into tumors and had no effect on accumulation of other leukocytes into tumors. In contrast, the VAP-1 inhibitors have been shown to significantly reduce only the number of proangiogenic and immune-suppressive Gr-1+ CD11b+ myeloid cells in melanomas and lymphomas, but its blocking had no effect on the number of other immune regulatory cells such as regulatory T cells and type 2 immune-suppressing monocytes/macrophages in the tumor [25]. However, VAP-1 inhibitors, but not anti–VAP-1 mAbs, retarded the growth of melanomas and lymphomas and reduced tumor neoangiogenesis. The VAP-1 inhibitors also reduced the binding of Gr-1+ myeloid cells to the tumor vasculature [20]. Furthermore, Tumor progression was reported to be retarded in VAP-1-deficient mice [26]. Application of anti-VAP-1 mAbs is not restricted to cancer. It has been revealed that a half-year long treatment with anti-VAP-1 mAbs targeting the VAP-1-positive microvessels in the pancreatic islets of NOD mice significantly decrease the incidence of diabetes without any adverse effects [27]. Interestingly, VAP-1 plays a very dominant role in migration of Th2-type, but not in that of Th1-type, lymphocytes to inflamed liver [28]. Use of small-molecule inhibitors to block VAP-1 might offer a new way to inhibit trafficking of Gr-1+ CD11b+ myeloid cells and inhibit tumor neoan-
giogenesis and tumor growth. This may be clinically relevant, because VAP-1 gene amplification has been found in gastric cancer patients and human tumor vasculature also expresses VAP-1 at least in the two cancer types (hepato- cellular carcinoma and head and neck carcinomas). Moreover, a soluble form of VAP-1 in serum may serve as a predictive marker in cancer because increased soluble VAP-1 levels were found in colorectal patients, and soluble VAP-1 proved to be an independent marker for predicting metastatic disease. [25, 26] Overall, the catalytic activity of VAP-1 is employed to recruit myeloid cells into tumor and to support its progression so that some researchers ([25, 26] and references therein) suggest that small-molecule VAP-1 inhibitors can prevent angiogenesis through a unique mechanism targeting immune cell trafficking, they alone, or in combination with therapies targeting vascular growth factors, might be useful for boosting antiangiogenic therapies.

Hypothesis

Some MDSCs (such as Gr-1+CD11b+ myeloid cells) exhibit T-cell suppressor function and may have a key role in maintaining immune homeostasis and protection from autoimmunity. It is noteworthy that several types of regulatory T (T<sub>reg</sub>) cells are the main controllers of excessive immune responses to foreign antigens. Proposed mechanisms to explain suppressive activity of the involved cells include the generation of inhibitory cytokines, induction of death in the effector cells by cytokine deprivation or cytolysis, local metabolic perturbation of target cells and finally inhibition of dendritic cell functions. According to previous reports, regulatory cells (if they can migrate to involved tissue) may suppress local immunity and accelerate tumor expansion. But, as mentioned above, blocking of VAP-1 had no effect on the number of regulatory T cells in the tumor [25]. Additionally, VAP-1 inhibitors reduce binding of Gr-1<sup>+</sup>CD11b<sup>+</sup> mononuclear cells (not T<sub>reg</sub> cells) to tumor vasculature and only affect infiltration and number of these types of proangiogenic myeloid cells in specific tumors (melanomas and lymphomas). So, it appears that tumors use the catalytic activity of VAP-1 to recruit some proangiogenic myeloid cells into tumors to support their progression. On the other hand, several studies have proposed that some autoimmune diseases are caused by impairment of the suppressive mechanisms involved in immunoregulation (see ref. 19 and references therein). Since (a) VAP-1 inhibitors have been recently proposed as potential new tools for cancer therapy; (b) CD11b<sup>+</sup> suppressive cells use VAP-1 mediated strategy for their adhesion and infiltration; (c) some CD11b<sup>+</sup> cells are believed to have a negative regulatory role in the development of autoimmune diseases; (d) it has been previously suggested that suppression of T-cell proliferation by some blood CD11b<sup>+</sup> cells requires cell contact (cell-cell interaction), [19] it is hypothesized that VAP-1 inhibition may interfere to infiltration of CD11b<sup>+</sup> cells (required for maintaining immune homeostasis in CNS) and lead to partial loss of suppressive function on immune system and therefore induce the development of autoimmune diseases like relapsing-remitting (experimental) autoimmune encephalomyelitis. Additionally, although the pathophysiological basis of multiple sclerosis (MS, as an autoimmune encephalomyelitis), is not entirely understood, several studies suggest that abnormalities both in the population of Gr-1<sup>+</sup>CD11b<sup>+</sup> suppressor cells and/or in the function of regulatory T-cells (occurred probably under the effect of the other suppressor cells, see ref. 19) may be the main contributing factors. Although MDSCs-mediated self-regulatory mechanism is disadvantageous in chronic diseases as well as in therapeutic settings based on repeated vaccinations, it could potentially be advantageous in controlling overshooting immune reactions as in autoimmune diseases (15 and references therein). In summary, Since VAP-1 mediates MDSCs recruitment in both tumor progression and protection from autoimmunity, there is the possibility that VAP-1 inhibition play a causative role in triggering onset of some autoimmune diseases, especially, in susceptible individuals administered by long-term VAP-targeted therapeutics (see scheme 1).
Scheme 1. Proposed schematic representation of cell migration through VAP-1 and its inhibition using small molecule inhibitors. (Left): Tumor cells produce some products that can cause to the accumulation of regulatory T cells into the site of tumor and lead to immune suppression locally. So, the tumor expands. (Right): Some specific leukocytes (such as CD11b+ myeloid cells), which use VAP-1 mediated strategy for their adhesion and infiltration, appear to be intrinsically suppressive and may have a key role in the protection from autoimmunity. Thus, it is hypothesized that VAP-1 inhibition may lead to the induction of autoimmunity.

References


