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Normalizing Function of Vessels in Desmoplastic Histopathological Growth Pattern, a Way to Restore the Immune Microenvironment in the Liver Metastases

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Abstract: *Solid tumors have the tendency to grow in normal tissue. By using hematoxylin and eosin (H&E) staining, the junction between solid tumors and normal tissue can be observed, revealing features such as vascular morphology. The histological growth pattern (HGP) of liver metastatic lesions can be categorized into two main types: alternative growth and connective tissue hyperplasia. Each subtype of HGP has distinct angiogenic patterns and immune cell infiltration statuses. The replacement histological growth pattern (r-HGP) grows directly around normal blood vessels without the need for neovascularization. Tumors with this pattern do not respond significantly to anti-angiogenic therapy or immunotherapy. On the other hand, the desmoplastic histological growth pattern (d-HGP) causes an inflammatory response in the junctional area between tumor cells and immune cells. The inflammation area promotes angiogenesis and suppresses immune cells. Controlled doses of anti-angiogenic therapy can improve vascular function in d-HGP and enhance the effect of tumor immunotherapy. However, this treatment option is only effective in d-HGP with disrupted vessels. Therefore, evaluating HGP in liver metastatic tumors is crucial before considering the combination of normalization of vascular function with immunotherapy.*

Keywords: *Liver metastases, Histological Growth Pattern (HGP), Normalization of Vascular Function Immunotherapy, Bevacizumab*

1. Introduction

When different types of tumor cells come together to form solid tumors, light microscopy can be used to observe the resulting morphological differences. These differences can reflect various microscopic characteristics of tumors, such as inflammatory cell infiltration and micro angiogenesis. These features are closely linked to the treatment response of tumors and patient prognosis. Histopathological growth pattern (HGP) is a morphological feature of a tumor that can be observed using light microscopy under H&E staining. It primarily indicates the boundary between the tumor and normal tissue. International consensus guidelines have been established for HGP of liver metastatic tumors. According to these guidelines, we can observe liver metastatic lesions and determine their HGP category. The main observed tissue growth patterns of liver metastatic lesions are alternative growth HGP (r-HGP) and connective tissue hyperplasia HGP (d-HGP). The main difference between these patterns is the degree of vascularization of neovascularization (Fig. 1)[8]. R-HGP mainly utilizes typical tissue structures through vascular co-selection, etc.; its vessels have an intact structure [2][3][4]; in contrast, in d-HGP, a circular inflammatory region at the tumor margin promotes neovascularization, and due to the persistence of high concentrations of inflammatory factors and VEGF in this region, most of the neovascularization is immature [2]. Immune cells cannot reach the tumor interior through these immature vessels to play their role in the immunosuppressive microenvironment of the circular border [6]. Controlled doses of anti-angiogenic therapy can normalize neovascularization, improve the hypoxic state of the tumor parenchyma, and reduce the inflammatory infiltration and immunosuppression between tumor and normal tissue [7], which can lead to a more significant role of immunotherapy of tumors.

In this review, we examine important features of HGP in liver metastatic tumors and explore the

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impact of these features on tumor treatment. Therefore, we emphasize the significance of a comprehensive assessment of tumor HGP prior to the integration of normalization of vascular function and immunotherapy.

2. Histopathological growth characteristics of liver metastases

Histopathological growth pattern (HGP) is distinguished by observing the demarcation between tumor and normal tissue using light microscopy under H&E staining, and the pathological characteristics of the entire lesion can be inferred from the HGP of a single lesion in a reproducible and reliable manner [1]. Morphologically observed, the differences between different HGPs are mainly in the degree of vascular function integrity and the growth pattern of tumor cells (Table 1), and some studies have also observed differences in the degree of lymphocyte infiltration in tumor tissue [2,3].

In replacement HGP, tumor cells grow infiltratively, similar to the process of replacing damaged degenerated cells with new cells in chronic liver injury [11,12], without significant immune rejection so that tumor cells can come into direct contact with normal liver tissue cells and hepatocytes in the hepatocyte panel are replaced by cancer cells. The blood vessels that were supplying normal tissues are also switched to tumor tissues by "vascular co-selection", a process in which the generation of new blood vessels is not essential [3,1314], which is undoubtedly a resistance mechanism for bevacizumab targeting angiogenesis [16,17,18]. It is noteworthy that lymphocyte infiltration is largely unobservable in slices of alternative HGP metastases [19], a phenomenon that has been described by some researchers as a "desert" immunophenotype [2,23] (Fig. 1c), precisely because the immune system does not recognize such tumor cells. Even if immune cells could match the tumor area, they would not be able to exercise any therapeutic influence. For this type of tumor, enhancing the immunogenicity of the cancer may be one of the treatment directions. It has been suggested that r-HGP may convert to d-HGP under the influence of neoadjuvant therapy [20], and unfortunately, HGP after this transformation no longer seems to have a predictive value for prognosis [21]. There are no further studies to confirm whether the change in HGP after neoadjuvant therapy is accompanied by a concomitant shift in the immune cell infiltration status and vascular growth pattern of the tumor tissue, which may have implications for the treatment of r-HGP metastases.

In connective tissue hyperplasia HGP, tumor cells rely on surrounding circumscribed connective tissue to push out normal hepatocytes, similar to fibrous proliferation following liver cell damage [10]. When immune cells come into contact with immunogenic tumor cells, they release a series of inflammatory factors and induce VEGF expression, attracting inflammatory cell infiltration and fibroblast proliferation to form a fibrous tissue encasing the solid tumor. The tumor cells of this HGP do not come into contact with each other, and the vasculature is characterized by a high percentage of immature neovascularization and much of the neovascularization is not covered by pericytes [2]. As the most critical signal to promote angiogenesis, vascular endothelial growth factor (VEGF) plays a vital role in the formation of these neovascularizations [3,5]; however, the continuous stimulation of VEGF also leads to difficulties in vascular maturation and increased vascular permeability, which increases fibrin deposition in the intercellular stroma [3], as well as a decrease in intraluminal pressure and an increase in blood viscosity due to massive leakage in the lumen. This leads to a reduction of the vascular transport of immune cells [9]. We can observe an extensive infiltration of lymphocytes in the connective tissue at the margins of d-HGP metastases. However, few lymphocytes can be found in the tumor parenchyma, a phenomenon described as an "excluded immune phenotype" [23] (Fig. 1d). We believe that this "exclusionary immune phenotype" is formed by two main processes; first, increased vascular permeability within the fibrous layer at the edge of the tumor parenchyma and chemotaxis of a large number of inflammatory factors in the junctional area lead to the filtration of many lymphocytes out of the tumor vessels and into the fibrous interstitium, which dramatically reduces the number of immune cells within the tumor vessels that could enter the tumor parenchyma; second, angiogenesis is always accompanied by immunosuppression, and a large number of VEGF and immunosuppressive inflammatory cells within the fibrous layer leads to the suppression of peritumor immunity. Like the appeal theory, patients with renal cancer undergoing anti-angiogenic therapy reduced neovascularization and increased the infiltration of CD8-positive T cells in the tumor parenchyma [24]. In immunotherapy of melanoma, treatment with bevacizumab in combination with immune checkpoint inhibitors resulted in a decrease in the infiltration of immunosuppressive macrophages in the tumor mesenchyme. At the same time, no difference in the appeal was observed when immune checkpoint inhibitors were used alone [25], which nicely demonstrates the immunosuppressive effect of VEGF from the reverse direction. Mesenchymal fibrosis in malignant tumors is closely related to angiogenesis, and similar to angiogenesis, fibrosis is usually accompanied by immunosuppression. For example, cancer associated fibroblasts

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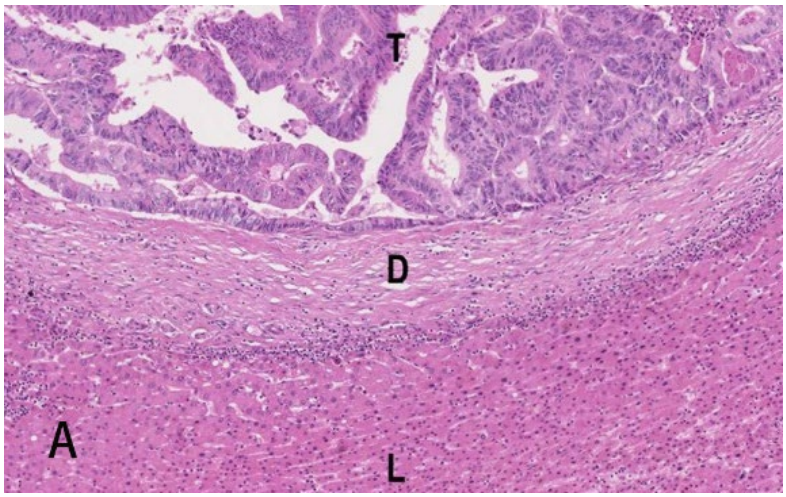
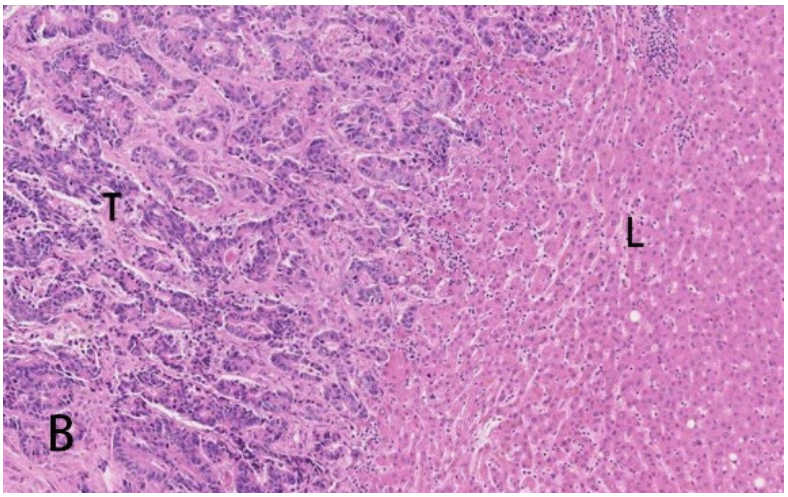
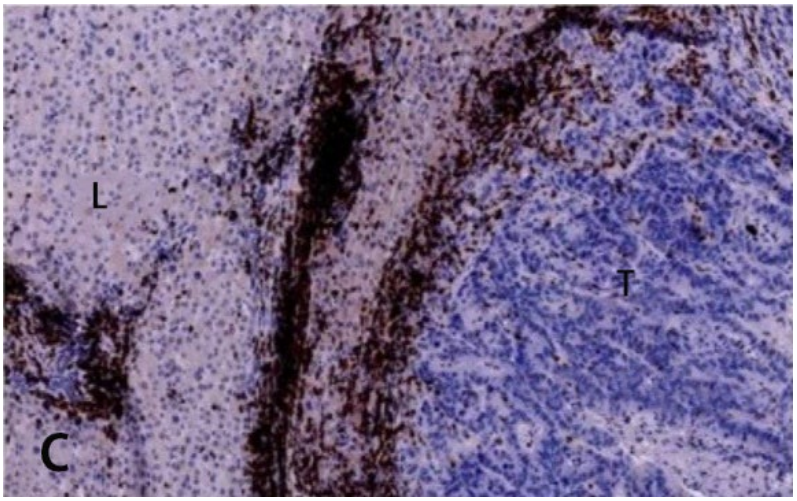
(CAFs) can secrete TGF-β, CXCL12, SDF1-α, etc. TGF-β is not only one of the essential fibrogenic factors that promote the proliferative response of connective tissue but also has a direct suppressive effect on the cellular immunity of T cells and macrophages [26,27]. CXCL12 initially plays a role as a chemokine [28][29] and is trimmed by DPP4 in the FAP family to act together with CXCR4 in immune rejection [30,31].







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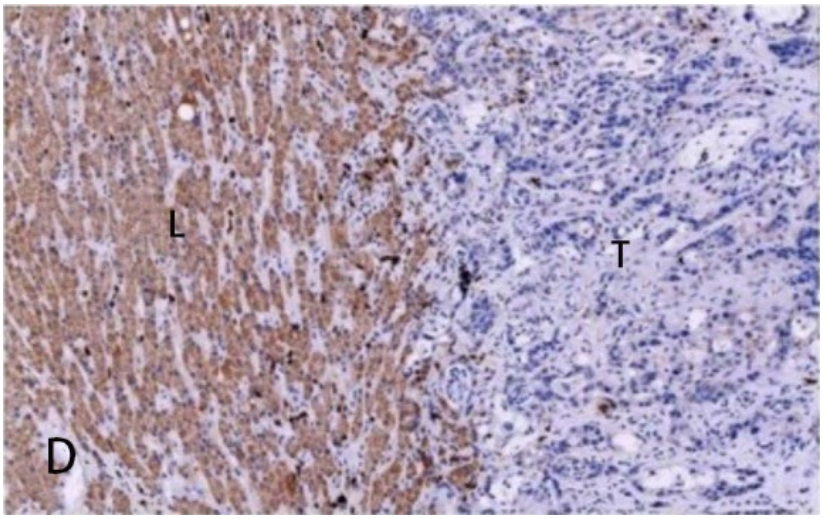

Figure 1 a and b are images of d-HGP and r-HGP liver metastases under high magnification after H&E staining. Figure. c shows a "desert" state with no lymphocyte infiltration in the tumor region in r-HGP, while Figure. d shows many lymphocytes accumulating in the junctional area with little lymphocyte infiltration in the tumor region, a phenomenon described as an "excluded" immunophenotype. This phenomenon is described as an "exclusion" immunophenotype. This phenomenon is described as an "exclusion" immunophenotype. (Fig. c and d were performed using the hematoxylin counterstaining method.) (T: tumor; D: desmoplasia; L: liver)

Figure 1: Images of colorectal cancer liver metastases with different HGPs. (Fig. a & b Preprinting with permission from reference [8] copyright 2019 Angiogenesis, Fig. c & d reference [23] copyright 2009 Cancer Immunity)

As mentioned above, r-HGP metastases have naturally mature blood vessels, and tumor growth and development do not depend on angiogenesis, so anti-tumor angiogenesis and normalization of vascular function treatment cannot be effective. Therefore, this review focuses on whether anti-angiogenic therapy and normalization of vascular function in d-HGP liver metastases can alter the immune cell infiltration status of liver metastases and enhance the immunotherapeutic effect. As mentioned above, r-HGP metastases have naturally mature blood vessels, and tumor growth and development do not depend on angiogenesis, so anti-angiogenesis and normalization of vascular function are ineffective. Therefore, this review investigates whether anti-angiogenic therapy and normalization of vascular function in d-HGP liver metastases can change the immune cell infiltration status of liver metastases and enhance the immunotherapeutic effect.

3. Normalization of vascular function and immunotherapy

As a key player in tumor angiogenesis, VEGF can promote immunosuppression through several pathways; firstly, VEGF can limit the T cell activation process by inhibiting the maturation of dendritic cells and blocking their antigen presentation process [15,32]; secondly, VEGF can stop the cytotoxic T cell activity and transport process, a process that is mainly mediated by regulating the T cell suppressive check achieved [24,33]; Finally, VEGF can act as a chemokine-like agent, causing Treg cells, tumor m2-like tumor-associated macrophages (TAM) and myeloid-derived suppressor cells to accumulate in the peritumor fibrous layer [35], acting as an "immune barrier" to the tumor (Fig. 2). Despite the presence of so many immunosuppressive effects, anti-angiogenic therapy against VEGF failed to improve patient survival outcomes in clinical trials [22]. It seems contradictory that while we can antagonize the immunosuppressive effects of appeal when using VEGF antibodies to block angiogenesis, we also lose access to drug delivery to the tumor as the tumor vasculature disappears.

Another issue of concern to us is the hypoxic state of the tumor, which results from the contradiction between the rapid energy consumption of the tumor and the weak trophoblastic vasculature [34]. In the early stage of tumor development, tumor cells always maintain a rapid multiplication, which requires ample energy and oxygen supply. In contrast, the tumor vasculature at this time is morphologically and functionally incomplete under the influence of the tumor microenvironment (TME) [36,37]. When the vascular supply cannot meet the tumor consumption, the tumor is always hypoxic, which may be related to hypoxia-induced tumor immunosuppression [38]. In this unfavorable TME, the rash use of adequate

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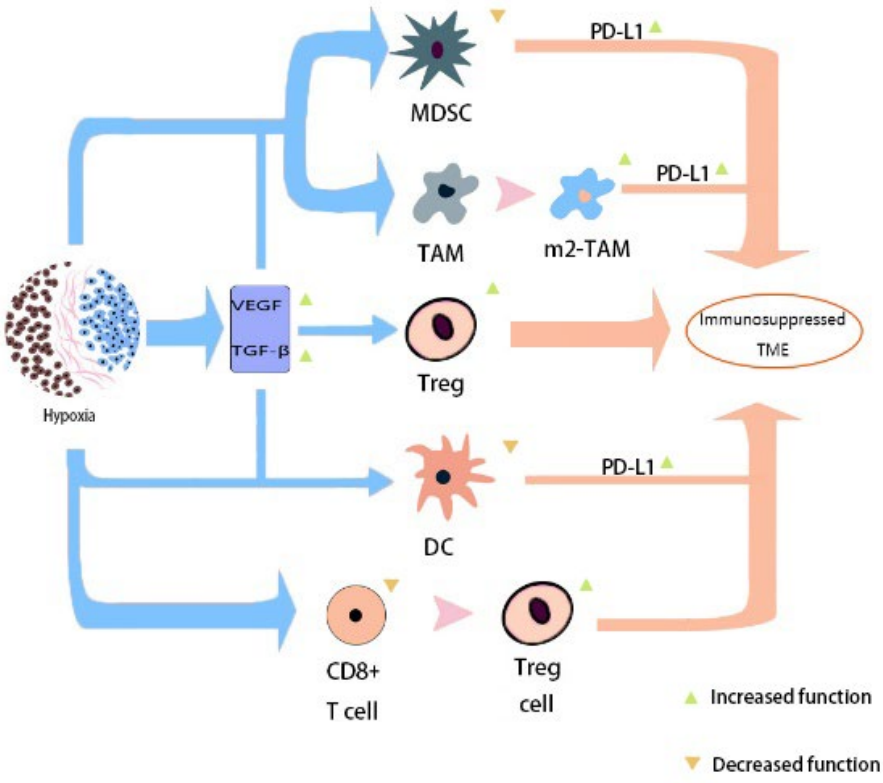
anti-angiogenic therapy would undoubtedly exacerbate tumor hypoxia and lead to an acidic TME [9], which would result in immunosuppression [40] (Fig. 2). In recent years, it has been continuously shown that tumor hypoxia and an acidic TME induce TAM migration and promote further TAM differentiation into m2-type TAM, which would suppress the immune action of T cells; instead of differentiating into cytotoxic m1-type TAM [41]. The lower expression levels of m2-like genes in tumors with good perfusion than those with poor perfusion were also observed by gene level [7]. In addition, hypoxia-inducible factor-1 (HIF-1) can act on TAM, myeloid-derived suppressor cells, and dendritic cells to increase the level of programmed death ligand 1 (PD-L1) expression [41,42]. Hypoxia can also lead to elevated levels of transforming growth factor-β (TGF-β) and VEGF, resulting in diminished dendritic cell function [32]. Furthermore, when T cells are exposed to a hypoxic environment, CD8+ T cells, which have a cellular immune effect, are suppressed, and, on the contrary, CD4+ regulatory (Treg) cell activity is increased [43]. In addition to the immunosuppressive effects of tumor hypoxia, it may also screen out less differentiated cancer cells through "hypoxia tolerance", increasing overall tumor malignancy [44,45]. Notably, hypoxia and acidic TME can also promote extracellular matrix (ECM) degradation and tumor cell migration through HIF-1-mediated biological processes [46,47], and epithelial-mesenchymal transition in cancer cells is also associated with hypoxia [39,48,49].



Hypoxia in tumor cells promotes the conversion of TAM to the immunosuppressive m2-type TAM [41], suppressing T cells' cytotoxic effects. In addition, hypoxia induces the expression of programmed death ligand 1 (PD-L1) in TAM, myeloid-derived suppressor cells, and dendritic cells, which directly leads to the inability of immune cells to recognize and kill tumor cells [41][42].

Figure 2: Immunosuppressive state in the tumor microenvironment due to hypoxia & VEGF.

As we have described, anti-VEGF therapy benefits patients, but excessive angiogenesis blockade can exacerbate tumor hypoxia and lead to poorer clinical outcomes; therefore, finding an appropriate anti-angiogenic dose may be vital to improving patient outcomes. Some researchers found that lower doses of bevacizumab resulted in more incredible clinical benefits for patients with glioblastoma than regular doses [51,52]. This is because the use of low doses of VEGF blockade avoids the problems associated with tumor hypoxia [7,36], and the use of regular doses of 1/8-1/2 VEGF blockade promotes normalization of vascular function without exacerbating tumor hypoxia [7,50].

To date, more and more studies have been published about the combination of anti-VEGF with immune checkpoint inhibitors, for example, in the treatment of hepatocellular carcinoma, where anti-

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vascular endothelial growth factor was found to act synergistically with anti-PD-L1 possibly by targeting angiogenesis, Treg proliferation, and myeloid cell inflammation [53]. Similar studies have also appeared regarding glioblastoma [54], malignant overlying mesothelioma [55], and even esophageal cancer [review [56], where corresponding applications have been made and clinically significant findings have been achieved; unfortunately, however, most the anti-VEGF agents used in the studies were not within the range of vascular normalization doses. We found few relevant studies in the direction of liver metastases for the time being. We can take advantage of the straightforward observation of liver tumors to obtain the HGP of tumors in advance and use appropriate doses of anti-VEGF for d-HGP to promote the normalization of vascular function and improve the hypoxic microenvironment of tumors. In that case, this will improve the immunosuppressive state of tumors and enhance the drug and immune cell transport capacity of tumor vessels, significantly improving the immune therapy effect. This not only improves the immunosuppressive condition of the tumor but also enhances the drug and immune cell transport capacity of tumor vasculature, dramatically improving the tumor's immunotherapeutic effect. It should be noted that this treatment may not be effective for r-HGP and may even cause delays in treatment.

4. Discussion

It is believed that tumors with different HGPs exhibit varying peripheral vascular conditions and immune cell infiltration statuses. This leads to differences in how r-HGP and d-HGP evade the immune system. While r-HGP tumor cells can deceive our immune system and avoid regulation by cytotoxic T cells, d-HGP tumor cells struggle to avoid recognition by immune cells and survive by excluding them. Maintaining a balance between inflammation and the signals that suppress inflammation and immunity is crucial for our body's immune system when inflammation occurs. The mechanism in question serves to protect the body from the damaging effects of "inflammatory storms." However, it also hinders the body's ability to eliminate tumors or chronic inflammation.

The crippled vasculature within the tumor junction zone and a large number of immunosuppressive factors are the main ways in which d-HGP liver metastases escape from immune killing [9,32,33], and hypoxia is also an essential factor in their immune tolerance [7,40]. It has been shown that appropriate low-dose anti-VEGF therapy normalizes vascular function and reverses the immunosuppressive state around the tumor [7], which may be a powerful weapon to break this immune barrier; in contrast, anti-VEGF therapy with regular doses may exacerbate hypoxia in tumor cells and produce an acidic tumor microenvironment, which may lead to worsening clinical outcomes in patients [44,45,46]. Combination therapy with bevacizumab and immune checkpoint inhibitors is receiving more attention in clinical trials [53,54,55]. However, few physicians use regular vascular doses of bevacizumab for combination therapy in clear tumor HGP, which may lead to improved treatment outcomes.

The challenge that needs to be addressed before such combination therapy can be achieved is how to assess the HGP accurately, and since the HGP is distinguished mainly by looking at the part of the tumor that borders normal tissue [1], even in the more easily distinguishable liver metastases, one can only expect an accurate assessment using light microscopy after tumor resection. Even more problematic is that the HGP of the tumor seems to change for a patient, as described by Boris Galjart et al. Some tumors transform from r-HGP to d-HGP after chemotherapy, but d-HGP, after the shift occurs, does not suggest a better prognosis [8]. Therefore, it is worth considering how to obtain the HGP type of tumor in a simple and noninvasive way. Fortunately, this dilemma is solved with the development of imaging techniques. Semelka and the research group found that transient perifocal enhancement on MRI images may suggest the possibility of d-HGP [60,61]. Yamaguchi and his colleagues compared the aspect ratios of tumor liver junctions on CT. They found lower aspect ratios for d-HGP tumors [57], and similar findings were made by Mentha et al. [58]. With the aid of artificial intelligence, Martijn P. A. Starmans et al. developed a machine-learning prediction model that is more accurate than manual judgment [59]. In addition, we hope that genetic or transcriptomic analysis of tumor cells with different HGP can be performed to expect more basis for assessment in genetic testing or immunohistochemical examination activities.

In conclusion, HGP scoring criteria for liver metastases are improving, imaging-based judgments are becoming more accurate, and HGP assessment is becoming more stable and accessible. The HGP of liver metastases is a morphological reflection of the different phenotypes of the tumor cell microenvironment, which is closely related to and interacts with angiogenesis, which leads to a state of immunosuppression around the tumor. We associate HGP, normalization of vascular function, and immunotherapy to provide a more precise therapeutic direction for immunotherapy effectively and a simple way to improve the immune microenvironment of tumors.

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Author Contributions

Yu Chen was responsible for most of the writing of this manuscript, and Yu Chen first proposed the direction of this study. Hao Cai, JianCheng Li and Hao Cai provided meaningful comments while writing the manuscript. HouJun Jia, the corresponding author, was informed about the article's writing from the beginning to the end.

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