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Editorial

Tumor Microenvironment Management: Can It Be the Solution to Cancer Treatment?

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Cancer treatment is one of the most critical health policies of many governments. Treatment methods as the first line of cancer treatment, including chemotherapy, radiation therapy, and surgery face many problems.[1] Although one or a combination of these therapies is still the first choice of many oncologists, their ineffectiveness in many patients has led to widespread patient frustration. These interpretations suggest that new treatment methods should be developed and evaluated.[2-4]

Various immunotherapy methods have been designed and evaluated for cancer treatment in the last two decades. Unfortunately, a number of methods have not had promising results and have finally failed to reach the clinical stage. Searching for the reasons for the ineffectiveness of these methods can be accompanied by many answers. Still, the most important explanation may be related to the nature of the tumor microenvironment.[5,6] Cancer cells in the tumor microenvironment do their best to ensure that all the factors necessary for their growth are available. In addition, they use many mechanisms to inhibit antitumor immune responses. These surprising characteristics of cancer cells in the tumor microenvironment seem to lead to the ineffectiveness of many immunotherapy methods. The advent of various treatments into the tumor microenvironment means their entry into a terrifying castle full of soldiers who intend to disarm the immune cells.[7,8] In most cases, the tumor microenvironment wins this unequal war. Therefore, many researchers involved in immunotherapy have realized that the tumor microenvironment conditions must be optimized to have successful immunotherapy. However, one of the most important questions that appear at this time is which component or mechanism management in the tumor microenvironment can have a more significant effect on the result of immunotherapy. The answer to this question may require a more detailed understanding of the types of tumor microenvironment.[9,10] Based on the new classifications, three types of tumor microenvironments have been introduced to date: hot tumors, cold tumors, and altered tumors.[11] Hot tumors have an inflammatory microenvironment and indicate extensive infiltration of T cells to the tumor area. In this category of tumors, immunosuppressive mechanisms are active, and these types of tumors respond better to various immunotherapy methods aimed at inducing antitumor-immune responses. Some tumors such as head, neck, melanoma, non-small cell lung cancer, kidney, and bladder are included in this category.[12] On the other hand, cold tumors refer to those in which the infiltration of T cells is not carried out inside the tumor; as a result, there is no news of inflammation inside the tumor. These tumors are typically not immunogenic and do not respond well to immunotherapy treatments, and common anti-cancer therapies have more priority in their treatment. In addition, surrounding these tumors by various types of immunosuppressive cells such as Treg and myeloid-derived suppressor cells (MDSC) inhibits the immune responses of cells approaching these tumors. Several tumors such as glioblastomas, ovarian cancer, pancreatic cancer, and prostate cancer are included in this category.[13] In 2019, a new category of tumors called altered tumors was also introduced, which itself had two types: altered–immunosuppressed and altered-immune excluded tumors. Although altered–immunosuppressed tumors are characterized by the scattered and small presence of immune cells (e.g., CTLs) around the tumor and the widespread presence of immunosuppressive cells around the tumor, altered-immune excluded tumors are characterized by the absence of immune cells around the tumor as well as the presence of hypoxia, and collapsed stroma is identified in the tumor.[11]

According to the above definitions, it is clear that a single immunotherapeutic prescription cannot be used for different tumors or different patients. This point makes the importance of personalized medicine more

clear. As a result, the future of tumor immunotherapy will face new challenges, including a more accurate understanding of the nature of tumors. Talking about the types of immunotherapy without considering the nature of tumors can be meaningless, and before designing any immunotherapy method, the conditions of cancer must be carefully and expertly checked. Now, iit can be understoodthat the reason for the failure of many immunotherapy methods may lie in neglecting to investigate the nature of the tumor and not trying to remove the obstacles of immunotherapy in cold or hot tumors. Therefore, I believe several points should be considered regarding designing and implementing various immunotherapies. First, the cancer's nature and the tumor type must be determined. If there is a hot tumor, immunosuppressive barriers should be removed to provide optimal conditions in the tumor microenvironment. Combination therapies, one arm of which can be checkpoint inhibitors, are examples of such strategies. On the other hand, when encountering cold tumors, mechanisms must first be used to convert the type of tumor to hot, and then the induction of immune responses can be a solution. For example, targeting hypoxia can be a solution in these cases. All in all, many untraveled paths are currently in front of us, which must be followed quickly and carefully to have a clearer picture of cancer immunotherapy.

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