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Mini Review

Macrophage-Based Versus T-Cell Based Cellular Immunotherapy: Do we still have a Chance against Tumors?

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After the development of CAR-T technology and their efficacy in hematological malignancies, cell-based therapy has been stablished as a promissory strategy to treat cancer. Initial strategies have focused on T cell, however, nowadays the scientific community have expanded the cell-based therapies to other immune effectors. Here we discuss how the use cell therapies based on macrophages have the potential to exploit their functional diversity in order to circumvent the main limitations of T cell-based approaches. In recent years, there have been an increasing interest for the development of cellular therapies to treat cancer. In this scenario, T cells have been the main focus of the majority of the strategies due to its specific cytotoxic properties [1,2]. To date, the most expanded and studied T cell-based immunotherapy are the adoptive transfer of tumor-infiltrating lymphocytes (TILs) and the chimeric antigen receptor T cells (CAR-T) [1,2]. Despite the improvements to these strategies that have been made, several reports indicate that the advances in CAR-T-cell treatment of solid tumors have been slow to date [3-5]. Also, despite the enormous efforts of the scientific community to develop T cell-based strategies, their success has been largely restricted to hematologic malignancies, with several questions still unanswered regarding their efficacy on solid malignancies [5-8].

There are potential reasons that explain such a poor response to T cell-based therapy in the solid tumor setting. First, effector cells must traffic and colonize the tumor microenvironment (TME). This process involves several steps: extravasation, chemotaxis, and stromal tissue penetration, which can differ substantially among tumor types. Engineered or not, once in the tumor, lymphocytes should migrate throw abnormal vasculature with reduced adhesion architecture and overpass dense cellular and stromal barriers [9]. Once in the TME, a second wave of unfavorable conditions dampens T cell functionality: acidic conditions, hypoxia, immune checkpoint ligands and a network of suppressive cells [10-13]. Third, the antigen and therefore the specificity itself, confer a classical problem: heterogeneous surface antigen expression on tumor cells could impact T cell functionality ranging from exhaustion due to chronic antigen exposure to evasion of T cell detection by absence of antigen expression and/or proper presentation by tumor cells. Developing novel strategies to engineer T cells in order to circumvent such limitations is a viable option. However, scientific community have also started to notice that such practical limitations highlight the feasibility of looking beyond T cells for potentially more suitable effector cells [1]. Following the hypothesis of expanding the arsenal of effector cells, the concept of chimeric receptors for cancer immunotherapy has been expanded into other lymphoid immune cell types, such as γδ Tcells, natural killer T (NKT) cells, and natural killer (NK) cells [14]. Even when such lineages confer advantages over conventional T cells, their principal limitation is the relatively low frequency in circulation and, in consequence, the

practical limitations associated to the number of cells needed for a maintained treatment.

Mechanistically, three main questions should be taken in consideration for developing a suitable therapy: How to reach the tumor? How to warranty a sustained antitumor activity over time? How to warranty a sustainable source of effector cells for a successful therapy?

Nowadays it is well recognized the critical role of macrophages in the origin, progression and cancer treatment [1,2]. However, the accumulated evidence suggest that direct targeting of mononuclear phagocytes has failed to promote significant clinical impact, suggesting that such strategies are unlikely to become stand-alone therapies and their opportunity rest in combination with other approaches [2]. Several ongoing trials may add important pieces of information regarding the effectiveness of macrophage/monocyte-targeting strategies in combination with other therapeutics [15]. Macrophages have emerged as an attractive candidate for cell-based therapies. They are immune cells with an extraordinary functional plasticity. Their functions include regulation of tissue remodeling and homeostasis, clearance of cellular debris, elimination of pathogens, and regulation of inflammatory responses in several contexts, including cancer [16]. Unlike other immune cells, macrophages exhibit several features that can be relevant to circumvent the above-mentioned tumor-associated limitations when employed as effector cells for cell-based immunotherapy. In general, three benefits of the use of macrophages as effector cells can be defined: (1) inherent ability to colonize inflamed tissues; (2) direct tumoricidal activity depending on the polarization program and (3) their role as antigen-presenting cells.

The ability to colonize tumor tissues by macrophages is supported by the fact that there is a constant trafficking of mononuclear phagocytes into the tumors, reason that contributes to the highly infiltration of macrophages in the TME, representing the main immune population in the vast majority of tumor types [2]. These properties confer to macrophages a superiority over T cells in terms of migration into tumors when used as antitumor effectors. In addition, they can be exploited as delivery of therapeutics (nanoparticles, cytokines, etc.) into the TME [2,17].

Macrophages have the potential to destroy tumors cells by direct cytotoxicity, mediating antibody-dependent cellular cytotoxicity, elicit vascular damage and tumor necrosis and activate other immune effectors. However, tissue-intrinsic properties at the primary tumor site or the metastatic niche determine macrophage features. Once in the TME, macrophages can be re-educated to a protumoral phenotype [1,2]. To circumvent such limitations, recent macrophages-based therapies rely on the genetic engineering to improve even the migratory capacity or the cytotoxic properties. These modifications potentiate their antitumor phenotype, which may lead to a sustainable antitumor response in terms of time and quality. A proper example are the CAR macrophages (CAR-M). These engineered cells, depending on the induced modifications, may combine the tumor-trafficking properties of myeloid cells, stable inflammatory proinflammatory phenotype (M1), macrophage intrinsic cytotoxic properties, CAR-mediated targeted antitumor activity and APC function, which provide them whit several tools to mount a multifactorial antitumor response [1,2]. It is important to consider that, in the case of CAR-M, there are two main contributors of their cytotoxic activity: macrophage intrinsic cytotoxicity, which is not specific for a given antigen, and the one resulting from the contribution of the chimeric receptor, that depends on the expression of the antigen by the tumor cells. Considering that a fundamental limitation for T cell-based approaches is the link between their functionality with the presence of the antigen, the intrinsic cytotoxicity of macrophages represents an advantage over T cells. Such independence of the antigen presentation by the tumor cells has two major implications for macrophage-based therapies: (1) A marginal influence of the resistance mechanisms of the tumor, particularly the ones associated to lack of the antigens and/or their presentation into major histocompatibility system as result of the tumor editing and (2) potential effect on tumors where lymphocyte infiltrate is absent or scarce. In addition, depending on the polarization status, macrophages can exhibit potent antigen-presenting cell properties. Enhancing APCs features of macrophages could also be important for the generation of tumor-specific adaptive response, thus potentiating the antitumor responses through the involvement of additional effectors [2].

Even though several features of macrophage biology highlight them as promising tools for antitumor cell-based therapy development, several issues still need to be addressed in order to increase their effectiveness. The high phenotypic and functional plasticity and the influence of the microenvironment on modulating such plasticity, highlight the need of better understand the TAM diversity at a single-cell level. When engineering of macrophages, the choice of receptors and signaling components to be modified is a critical step to be consider. There is still limited understanding of replenishment rate, survival time, retention time of desired functional properties and the spatial distribution of the intratumoral macrophages. From a practical point of view, a pivotal component that influences the successful transit of macrophage-based cell therapies to the clinic is the development of novel, scalable and reproducible manufacturing process in order to generate high number of effectors to warranty a sustainable therapy. The use of macrophages as effectors in cell-based therapies gives the possibility to combine the intrinsic antitumoral properties they exhibit under certain conditions with novel features that could be enhanced using engineering strategies. The convergence of all these properties provides macrophages whit several tools to mount a multifactorial antitumor response and highlight the rationale for the development of novel approaches of macrophage-based cellular therapies. The understanding of how to efficiently combine such properties will significantly expand their therapeutic potential.

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Conflict of Interest

No Conflict of Interest.

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