Allogeneic Dendritic Cells in Cancer Immunotherapy: A Clinical and Experimental Perspective

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Cancer Immunotherapy

Cancer immunotherapy is facing times of tremendous recognition and has become a clinically validated option for many cancers [1,2]. The major immunotherapeutic breakthrough in efforts to eradicate malignancies came with the development of immune checkpoint inhibitors which re-energize cancer-specific T-cells [2]. Although effective against certain malignancies the majority of cancer patients do not benefit from checkpoint inhibitors [3]. To work, they require the pre-existence of cytotoxic CD8+ T cells recognizing Tumor-Associated Antigens [TAA]. It is evident that some form of cancer vaccine is needed to induce such TAA-directed T cells in cancer patients where checkpoint inhibitors are not yet working. Dendritic cell (DC)-based immunotherapy is a strategy to provoke T-cell-mediated anti-tumor immunity by taking advantage of the antigen-presenting capacities of these cells [4]. Autologous DCs can be manipulated to present Tumor-Associated Antigens [TAs] when injected into cancer patients, in order to prime naive cytotoxic CD8+ T cells against malignant cells.

Initially efforts to vaccinate with DCs were based on the direct presentation capacity of such cells, which were expected to migrate to lymph nodes and prime CD8+ T cells. However, this type of vaccination has low objective tumor-response rates [5]. Accumulating evidence argue that it is the bystander host DCs, instead of the injected TAA-loaded DC, mediating the priming of CD8+ T cells [6,7]. In the paper by Liu et al. autologous DCs, by acting as immune enhancers, orchestrate the recruitment and activation of bystander DCs and Natural Killer [NK] cells through the secretion of pro-inflammatory factors, in order to prime CD8+ T cells. This capacity of DCs to secrete immune cell recruiting factors has also been observed during viral infections, where infected cells can cross-talk and activate non-infected bystander DCs in order to prime functional T-cell responses [8]. Notably, the secretion of pro-inflammatory signals as a third signal during priming of tumor-specific T cells is among the key criteria imposed by a consensus for the production of successful cancer-vaccines [5,7]. Though initially it was expected that these secretory capacities were related only to direct T-cell polarization and activation, stimulation of other immune cells including bystander DCs can occur.

Laurell et al. utilized this bystander-DC need by developing an allogeneic cellular adjuvant based on pro-inflammatory DCs from a donor unrelated to the recipient (alloDCs) [10]. Their approach is based on the fact that DC-precursors can be programmed to strongly secrete immune cell recruiting and activating factors [11,12]. Importantly, the secretion of pro-inflammatory factors can activate immune cells independently of Major Histocompatibility Complex (MHC) compatibility [8,13]. Thus, the use of alloDCs offers the possibility to develop a cellular adjuvant as an off-the-shelf immunotherapy, targeting the local bystander immune cell activation. In addition, MHC-incompatibility introduces several T-helper type 1 (Th1) cytokines at the vaccination site which will be produced during the alloresponse towards those cells [13]. Interestingly, the concept of using allogeneic cells to induce tumor-immunity has also been described more than a decade ago as an alternative way to generate an immune-stimulatory environment in order to directly activate cross-reacting TAA-specific T cells [14].

In the study from Laurell et al., alloDCs from an unrelated donor were matured in the presence of Toll-like receptor ligands and IFNγ and subsequently injected in the tumor lesions of Metastatic Renal Cell Carcinoma (mRCC) patients. Their findings indicate that intra-tumoral administration of alloDCs is capable to induce T-cell mediated anti-tumor responses and it might also prolong survival in mRCC patients. The local administration of pro-inflammatory alloDCs is suggested as very potent inducer of immune cell recruitment and activation by the ability of activated DCs to secrete pro-inflammatory chemokines and cytokines in a sustained fashion. Therefore it is speculated that injecting alloDCs intratumorally will ignite a general immune cell activation and more importantly will recruit bystander DCs into the tumor [10]. Bystander-DC activation is particularly important in view of another key criterion for the production of successful cancer-vaccines, the incorporation of immunodeterminant TAAas in order to mount tumor-specific T-cell responses [5,9]. The intratumoral vaccination of alloDCs will take advantage of the local supply of TAAas, including mutation-derived neoantigens, as a source for the recruited host bystander DCs. The later will acquire antigens from their surroundings, mature due to the pro-inflammatory milieu and prime cytotoxic T-cell responses in the draining lymph nodes. Recently, patient-tailored neoantigen-based cancer vaccines have been proved therapeutically-potent
in boosting effector responses and control the disease [15,16]. This method is patient-tailored, meaning DNA from each individual tumor needs to be sequenced, TAAs and neoantigens need to be determined and their binding capacity to MHC needs to be predicted. This leaves a crucial gap between the identification of a possible treatment and the administration of it to the patients. On the contrary, alloDCs because they function as an adjuvant and utilize the tumor-burden in situ, they can circumvent this time-consuming preparation step. This novel concept is particularly interesting as it reverses the time-consuming “patient-tailored production” to an “off-the-shelf” therapy. It is also of great interest to speculate that the alloDC vaccination in combination with checkpoint inhibitors might result in synergistic antitumor effects.

References


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