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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 [TAAs] 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 [5,9]. 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 TAAs in order to mount tumor-specific T-cell responses [5,9]. The intratumoral vaccination of alloDCs will take advantage of the local supply of TAAs, 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.

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