Editorial

When the inhibitor is turned into stimulator: novel aspects in T cell engineering

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The therapeutic use of T cells for tumor immunotherapy encompasses isolation of T cells from the patient, arming T cells with a receptor conferring tumor-specificity and reinfusion to the patient (1). Equipping T cells with fully synthetic receptors consisting of the variable fragment of an antibody and of T cell activating domains, so called chimeric antigen receptors (CAR), has been investigated in several indications (2). CAR T cells directed against the pan-B cell antigen CD19 have proven efficacy in refractory acute B cell leukemia (ALL) and diffuse large B cell non-Hodgkin lymphoma (DLBCL) (3,4): in these difficult to treat patient populations, with a dismal outcome at historical follow-ups, CAR T cells have led to remarkable remission rates up to 81% and 54%, respectively. Phase 2 studies in these indications have revealed durations of responses with survival rates of 76% and 52% at 12 and 18 months, respectively. These unparalleled results have led to approval by the American Food and Drug administration (FDA) of anti-CD19 CAR T cells for refractory ALL and DLBCL in 2017.

Based on the reported outcomes, one is tempted to consider the treatment challenge of refractory B cell malignancies re solved by CAR T cells. The aforementioned studies were censored too early to speculate on the impact on overall survival, it is important to notice that most patients had already suffered disease recurrence at the time point of reporting. The MSKCC has recently reported the long term outcome of a patient ALL population treated with anti-CD19 CAR T cells of a slightly different design. In the cohort consisting of 53 patients, the median relapse free survival was 6 months and the median overall survival 13 months (5). With similar response rates, this cohort may be comparable to those included in the two pivotal studies above. This would conclude that anti-CD19 CAR T cells alone do not cure most patients. While available data confirms the principal value of T cell therapy in hematological malignancies, these recent reports also urge for additional strategies to enhance function of T cells.

In a recent issue of *Blood*, Oda and colleagues have reported on a novel immunomodulatory fusion protein (IFP) linking the extracellular domain of CD200R to CD28 to turn T cell inhibition into T cell costimulation (6). Comparing different IFP designs—by varying the transmembrane domain and extracellular portions of the protein—the authors demonstrated that the most effective design was the one allowing for dimerization of the IFP in the immunological synapse. CD200 positive leukemia cells induced additional activation and proliferation of the IFP-transduced T cells in synergy with the T cell receptor mediating leukemic cell recognition. In animal models, enhanced anti-leukemic activity was demonstrated which was independent of additional interleukin-2 supply, the later probably originating from the additional stimulation via CD28 signaling. Confirmatory findings using human T and leukemia cells support the translational value of the strategy.

Other groups and our own have previously reported IFP including fusion proteins of PD-1 or CTLA-4 to CD28 for directed conditional costimulation and enhanced efficacy of

T cell therapy (7,8). The CD200R-IFP now complements this arsenal for adoptive T cell therapy. The advantages of IFP over mere integration of CD28 into a CAR or TCR design are three-fold: (I) costimulation only upon simultaneous engagement of the T cell target antigen and the IFP ligand, potentially conferring enhanced safety and efficacy; (II) shielding of T cells from inhibitory signals, with the IFP also acting as a sink for suppressive ligands; and (III) no alteration of regulatory mechanisms in the T cell *per se* such as deletion of suppressive signals (e.g., knock-down of PD-1) which poses additional safety concerns. The novelty of the described construct is that it addresses a comparably understudied and little characterized immune check point molecule. The CD200R-CD200 axis may come with more disease specific aspects, as it confers a less favorable prognosis when expressed by the leukemic cells. Arguably, protumoral functions of the axis have also been reported in melanoma and other diseases, albeit not due to T cell interactions (9).

At the same time, this publication also raises several issues that will need to be resolved for further utilization and advancement of the field: first, the authors claim that dimerization and entry of the IFP into the immunological synapse is key to optimal function. This argument is based on a comparative approach where different IFP have been compared head to head functionally. However, the necessity of dimerisation has been previously challenged by others (7,10,11) and it is unclear if this property might rather be proprietary to CD200-CD200R interactions. Second, what is the requirement in terms of CD200 expression for functionality of the concept? Leukemic cells express CD200 but in non-hematopoietic malignancies most of the CD200 found, might localize to the stromal or infiltrating cell compartment. It remains to be clarified if responses would also be seen in such an expression pattern. Third and lastly, it must be further investigated if the growing number of functional IFP is interchangeable, if some might be more potent than others and, in particular, if there is a disease specific functionality. As different immune suppressive pathways might play non-redundant roles in different tumor entities, such knowledge would help prioritize the development of IFP for certain indications and clinical situations.

In summary, CD200R-CD28-IFP is a novel tool to fuel costimulation of genetically engineered T cells for cancer therapy. Future studies will need to clarify if the lessons learned from the design can be applied in a broader fashion and if this IFP will be of value in non-hematologic malignancies.

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