Editorial overview: Tumour immunology: Are we on the path to win the battle against cancer through immunotherapy?

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In the past several years we have witnessed renewed hope and optimism for the treatment of metastatic cancer through advances and discoveries in the field of tumor immunity and immunotherapy. Although the trend is towards finding effective curative strategies, by no means are we there yet, therefore, instead of letting our guard down and celebrate, we need to focus and learn more from the discoveries that have been paving the road for better and more targeted and effective strategies to ensure lasting remissions, and in an ideal case complete elimination of cancer, while minimizing the collateral damage. This collection of reviews presented in the section of Tumor Immunity highlights the significant advances made in the field, and potential new directions which should help advance the field and bring us to the finish line. After all, we should not forget that the beneficiaries are all those who have valiantly fought against cancer, and are looking up to the scientific community for treatments that are not only effective in curing their cancer but also allowing them to enjoy a good quality of life. On the road to achieve this, I would like to highlight factors that were found to be important for our search towards effective immunotherapeutic strategies. In this review collection, Drs Yee, Adusumilli and Debets discuss the prospects for effective adoptive T cell therapy (ACT). ACT is represented by three major modalities: tumor-infiltrating lymphocyte therapy, CAR-T engineered cell therapy and endogenous T cell therapy. CAR T cell therapy directed to CD19 demonstrated remarkable efficacy and long-lasting benefit for B cell malignancies. However, its use in other malignancies has been less than desirable, although moderate increases in survival periods have been reported in certain malignancies. Lack of an ideal antigen-target, in addition to heterogeneity in antigen expression is suggested to pose challenges for successful CAR T-cell therapy for certain cancers. To improve on the prospects of effective CAR-T therapy for other malignancies, investigators have turned to next generations of CAR-T cells with dual antigen-targeting CARs, tandem CARs, or switchable CARs, in conjunction with inhibitory CARs. Such modifications are not only important to increase the efficacy but also the safety of CAR-T cell therapies. Strategies to enhance Adoptive T cell therapy will likely incorporate other modalities such as immune check-point blockade, agonist antibodies, and vaccines in the future. In this regard Drs Pawelec and Berzofsky discuss the recent advances and major limitations in immunotherapy of cancer using check point inhibitors and vaccines.

Renewed and significant interest in adoptive NK cell therapy has generated quite a lot of enthusiasm among NK cell biologists in recent years due to several important factors. A key discovery in this front was to demonstrate the ability of NK cells to target cancer stem cells and poorly differentiated tumors that lack or express very low levels of MHC class I, since these tumors are less likely to be targeted by the T cells. It is also known that...
cancer patients have significantly suppressed NK cell numbers and function and indeed, it is very difficult to find NK cells in the tumor microenvironment of progressing cancers. The latter finding should, by no means, be interpreted superficially to indicate a lack or a minor role for NK cells in eliminating cancer. Indeed, quite the opposite: it should be considered as one of the major factors responsible for the progression of cancer. However, limitation in the expansion of NK cells to sufficient numbers for clinical use, inability to fully understand and appreciate the immunobiology of these cells, and lack of sufficient resources for the studies of NK cells in comparison to the other immune effectors have traditionally hampered the progress in the field of NK cells. We, in addition to Drs Rezvani and Wu, discuss advantages and limitations of novel immunotherapeutic strategies in the field of NK cells highlighting the significance of CAR-NK cell therapy, use of antibodies to NKG2D ligands and strategies to expand supercharged NK cells at the clinical scale for treatment of cancer among other important areas of NK cell therapy in cancer.

NK and T cells have to operate within a very complex and immunosuppressive tumor microenvironment. Drs Gabrilovich, Ostrand-Rosenberg, and Baniyash highlight the suppressive effect of myeloid derived suppressor cells (MDSCs), and discuss their suppressive role in cancer, even though the diversity and plasticity of MDSCs are found to be beneficial in autoimmune diseases and allo-genic transplantsations. To this end, tumor infiltrating fat cells and fibroblasts which constitute important components of stromal cells may not only shape the numbers and function of MDSCs, but also effect the function of other important effector cells such as T regulatory cells, dendritic cells, gd T cells, NKT cells and ILCs. On this front, Drs Ostrand-Rosenberg and William Murphy discuss the immunosuppressive effect of obesity and its role in cancer. Indeed, recent work from our laboratory indicates that obesity in combination with genetic alterations in pancreatic cancer is driving force for NK cell immuno-suppression at the preneoplastic stage of tumorigenesis.

Dr Garrido discusses the transition from HLA-I positive to HLA-I negative tumor phenotype during cancer progression which correlates with the decline in the number of tumor infiltrating T-cells, and possibly NK cells, and the establishment of a granuloma-like structure composed of only HLA-I negative tumor cells surrounded by a fibrous capsule. Such a scenario could also be interpreted as the selection of stem-like/poorly differentiated tumors, since these tumors do not express MHC class I, due to the loss of NK and T cell immune effectors which have capability to drive differentiation of such tumors.

Dr Karin discusses the significance of chemokine receptors and their ligands in tumor suppression. He indicates that a limited repertoire of chemokines direct the polarization of CD4+ and CD8+ T cells and highlights the significance of CXCL10 as a driver chemokine for CD4+ and CD8+ T cells. Without the ability to recruit NK and T cells to the tumor microenvironment, immune effectors will not be able to lyse nor will they be able to differentiate tumors. Both functions of NK and T cell immune effectors are imperative for the effective control of tumor growth.

Dr Sautes-Fridman discusses the prognostic significance of different subpopulations of tumor infiltrating immune cells within the tumor microenvironment. She identified negative prognostic characteristics in renal cell carcinoma patients based on the functional capability of tumor infiltrating lymphocytes (TILs). Such characterizations may facilitate the identification of patients with a high risk of progression in distinct cancers using peripheral blood leukocytes.

Finally, Dr Fong introduces therapy with oncolytic viruses as an important immunogenic therapy against cancer which, in combination with immunotherapy, may result in better containment of cancer. He further discusses the prospects of oncolytic virus therapy in modifications of immunologic landscape of tumor milieu from ‘cold’ to ‘hot’, and proposes the use of such therapy in combination with check point inhibitors, CAR-T/CAR-NK, tumor vaccine, and NK therapy.

There is no doubt that new approaches to cancer immunotherapy are revolutionizing how we understand and treat cancer. However, the idea of cancer immunotherapy is not new since many decades ago, the influence of immune effectors in cancer therapy was shown and appreciated in different tumor models. Because of a lack of an in depth understanding of how different immune effectors work together and with the tumor microenvironment in order to shape and either drive or impede cancer progression, many proposed and tested immunotherapeutic strategies were found to be less than desirable and at times completely ineffective. We are now starting to understand and appreciate the complexity of the tumor microenvironment, and the role of each of the major players in the orchestration of either the progression or cessation of tumor growth. However, as mentioned above we are not there yet. We need to fully understand the combinatorial work of all the immune effectors within the tumor microenvironment and appreciate the contribution of each and every effector to the process. We need to allocate adequate resources to the studies of all the important players of tumor microenvironment regardless whether we believe or think that they have more or less significance in the elimination of cancer, because we may be surprised to find that those which we have thought to have no or low representation in the tumor microenvironment may end up having a greater role in the containment of cancer. The collection of reviews presented in the
section of Tumor Immunity not only highlights our progress towards finding effective and lasting treatments for cancer, but also discusses the challenges ahead. The ultimate collective goal of the scientific community should not only focus on finding lasting remissions and cures for cancer, but also in ensuring that through the process the quality of life is not sacrificed in cancer patients.