Future perspectives
Personalized cellular approaches

Increasing insight in tumor biology has given us more treatment options and more information about individual patients. To treat a patient optimally it would be preferred to know as much as possible about the molecular and cellular composition of individual tumors. Through increased technology we are now better capable of identifying TAA specific T cells [1,2]. T cell receptors recognizing TAA can be used to genetically engineer large amounts of T cells capable of recognizing tumors [3]. This technique has not yet lead to clinical successes. An immunotherapeutic approach like adoptive cell transfer with autologous TIL has already been shown to be effective [4]. The success of this TIL treatment was largely dependent on the telomere length and number of CD27+ CD8+ T cells in the TIL infusion. By using autologous TIL the identification of TAA is not necessary. The emphasis of this type of treatment is on the general characteristics of the TIL; high number of CD8+ T cells together with a ‘young’ (CD27+/CD28+) phenotype for a long lifespan enhances the anti-tumor effect [5]. Unfortunately, it is very costly to provide each individual patient with their own personalized treatment. Especially if we consider the number of cancer patients it is expected to increase in the next decades. It would therefore be wise to consider treatment options that can be implied on large groups of patients using more general information about the tumors.

Antibodies

T cells have the intrinsic capacity to kill tumor cells, however, in and around a tumor T cells can be less adequate at killing tumor cells. The presence of CTLA-4, which becomes expressed after T cell activation and functions as a natural break to prevent autoimmunity can prevent cells from killing tumor cells. Ipilimumab is a novel antibody that binds to CTLA-4 and thereby blocking the ability of CTLA-4 to inhibit T cells function. This antibody is not directed against the tumor cells but is aimed at enhancing the immune response against the tumor [6]. It is an appealing candidate for adjuvant cancer therapy and has been tested in patients with melanoma or prostate cancer [7,8], increasing the overall survival of melanoma patients compared to other therapies [9,10]. Since CTLA-4 has proven successful, other types of monoclonal antibodies directed to release the brake of the T cell are being investigated as well. Antibodies directed against PD-1 and PD-L1 have lead to clinical responses in melanoma, NSCLC and kidney cancer patients [11]. Such strategies might be worthwhile to investigate in the treatment of various cancer patients since it removes the naturally occurring inhibition following activation of T cells.

Strategies aimed at boosting the immune system are only useful if enough T cells are present to elicit an anti-tumor response. We found that CRC patients with MSS tumors who have low immune infiltrates do not benefit from the boosting capacity of ASI treatment [12]. Although it has not yet been proven, the presence of a certain number of T cells in tumors of patients receiving monoclonal antibodies like ipilimumab and anti-PD-1 is crucial for this treatment to work as well. To a lesser extent TIL therapy also requires a certain amount of immune infiltrate. For patients with low tumor immune infiltrates therapies using genetically engineered T cells (derived from peripheral blood T cells) could be a worthwhile alternative.
References


