ImmunoTools *special* Award 2014

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Activation of human NK cells to overcome mechanisms of drug resistance in hematological and solid carcinomas.

During the last years immunotherapy has emerged as a good alternative for the treatment of hematological and solid carcinomas that do not respond to conventional treatments such chemotherapy, radiotherapy or biological modulators. Monoclonal antibodies against mutated or overexpressed membrane tumor antigens have been proved to be efficient for the treatment of specific hematological malignanices (i.e. Rituximab in lymphoma) and carcinomas (i.e. Trastuzumab in breast cancer). In addition, new mAb with immunostimulatory activity (i.e. Ipilimumab or Nivolumab) have shown a good activity for the treatment of recurrent melanoma and some types of lung carcinoma. Despite these advances, still a high number of solid carcinomas that do not respond to conventional therapies and mAb remain incurable.

Our group is interested in understanding the molecular mechanisms involved in the elimination of transformed cells by Cytotoxic T (Tc) and Natural Killer (NK) cells (Pardo et al. Eur J Immunol 2002, J Cell Biol 2004, Cell Death Diff 2008; Herz et al Nat. Immunol 2009; Arias et al. Cell Reports 2014) in order to exploit such a potential to treat highly resistant cancer cells. Using mouse in vivo/ex vivo models we have found that killer cells mainly use the serine protease granzyme B to kill transformed cells, overcoming viral as well tumor strategies to block cell death (Pardo et al PLOs One 2009; Cell Death Diff 2008; Aguilo et al Immun Cell Biol 2010). Based on these in vivo mouse models we are now translating our findings to the human system by analysing the potential of NK cells to overcome multidrug resistance in hematological neoplasia and solid carcinomas.

In recent years the use of allogeneic NK cells to treat recurrent hematological neoplasias has emerged as a promising alternative for these patients increasing considerably the life expectancy (Velardi et al. Curr Opin Hematol. 2012; Locatelli et al. Front. Immunol 2013; Miller et al. Biol Blood Marrow Transplant, 2009). Still its potential in the treatment of solid carcinomas remains obscure.

Our group have recently found that activation of allogeneic human NK cells using different protocols produces changes of the NK cell transcriptome, which could affect the quality of the NK cells generated, including its cytotoxic potential against target cell (Sanchez-Martinez et al. Int J Biochem. Cell Biol. 2013). Indeed only NK cells activated under specific conditions were able to overcome drug resistance in selected hematological tumours.

We plan now to find out the best condition to expand and activate human NK cells in vitro to efficiently kill different hematological and solid carcinomas including the population of cancer stem cells responsible for cancer resistance and recurrence. To this aim we plan to use different cocktails of cytokines and/or accessory cells to expand the NK cell population in PBMCs cultures. Activated NK cells will be phenotypically and functionally characterised including the expression of surface markers, the production of cytokines like IFNg and TNFa and its ability to kill primary and established cancer cell lines as well as healthy cells, including the combination of activated NK cells and mAb currently used in cancer therapy.

Our results will help to design novel therapeutic treatments to kill hematological and solid cancers for which there are not other treatments alternatives.