HER2-MEDIATED T CELL KILLING IS INFLUENCED BY THE INVERSE CORRELATION OF TARGET VS MHC CLASS I EXPRESSION ON BREAST CANCER CELL LINES IN VITRO

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Background Beyond its role as direct therapeutic target in oncology HER2 is gaining more and more importance in immunotherapeutic treatments that aim to facilitate the engagement of cytotoxic T cells with the tumor cell. Recent reports have indicated that there is an inverse correlation between HER2 and MHC Class I expression. To understand the impact of this correlation on treatment options for patients we tested two HER2+ cells lines sensitivity towards HER2-mediated T cell-based therapy.

Methods We developed an in vitro protocol to generate antigen-specific CD8+ T cells by priming on HER2+ breast cancer cell lines JIMT-1 and SKBR-3. Subsequently, these primed CD8+ T cells were tested in 2D and 3D immune cell killing assay in a life cell imaging device in combination with an endpoint viability assay. The activity was compared with unspecific CD8+ T cells activated by phytohemagglutinin (PHA) or αCD2/αCD3/αCD28, HER2-peptide specific T cells and HER2-CAR T cells serving as a positive control. All cellular therapies, except for the HER2-CAR T cells, were tested as monotherapy and in combination with trastuzumab (anti-HER2 antibody).

Results The antigen specific CD8+ T cells displayed a significantly improved killing potential of JIMT-1 cells in 3D, which is in line with the upregulation of MHC Class I in 3D vs 2D for this cell line. Interestingly, the antigen-specific cells displayed the highest killing potential compared to the otherwise activated T cells. The combination with Trastuzumab did not influence the sensitivity towards the different cell therapies, which is in line with the reported Trastuzumab-resistance of the donor patient of JIMT-1. In case of the SKBR-3 cells the antigen specific CD8+ T cells were the most effective therapy in 2D as well as in 3D. The combination with trastuzumab displayed improved killing in 2D due to the upregulation of MHC Class I when HER2 signalling is blocked.

Conclusions In summary, our study showed that the efficacy of the different T cell therapies was driven by specificity to the targeted tumor cell and the expression of MHC Class I. The latter is influenced by the culture condition as well as the modulation of the HER2 signaling pathway. We will further elucidate the influence of both components by modulating the culture condition via the addition of fibroblasts and blocking the HER2 pathway through small molecules that at downstream of HER2.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0883