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Immune deficiencies in breast cancer. C. Wiltschke, A. Budinsky, C. Kichler-Lakomy, CC. Zielinski

The importance of immunological deficiences for the development and progression of cancer has been in controversial discussion for years, in particular whether these alterations are the result or the cause of the malignant disease. Nevertheless, convincing data are scarce. We have previously shown, that patients with breast cancer have several impaired immunological functions (reduced mitogen/antigen stimulation, reduced monocyte functions, reduced cytokine production) and that some of these deficiences are also found in patients with early breast cancer (EBC) or even in healthy females with germline mutations of BRCA1.

We have now expanded our investigations to dendritic cells (DC). DCs derived from patients with EBC presented with a significantly reduced expression of DC-associated antigens CD1a (p=0.02), CD83 (p=0.0001), CD80 (p=0.01), CD86 (p<0.0001) and CD54 (p<0.0001), as compared to DCs derived from healthy control females. Moreover, CD3- CD4-CD8- DCs derived from the latter patient population had an obviously aberrant expression of costimulatory molecule CD28. In contrast, no significant differences in the expression of CD1a, CD54, CD80, CD86, CD83 and CD11c were observed between DCs derived from healthy women with germline mutations of BRCA1 and healthy control women (p>0.05). Finally, T cell-proliferation in response to TT-pulsed autologous DCs was significantly decreased in patients with EBC (p=<0.0001).

Conclusions: DCs derived from patients with EBC had not only an immature and aberrant phenotype, but also functional impairment in TT presentation which was not detectable prior to the development of disease in high risk individuals.

Generation of HER2-reactive T helper and T killer cells: Implementation for T cell therapy

Helga Bernhard, Christian Meyer zum Büschenfelde, Burkhard Schmidt, Jochen Metzger, and Christian Peschel

Attempts to eradicate cancer by adoptive T cell transfer have been limited due to the difficulty of generating T cells with defined antigen specificity. The current study focuses on the generation of cytotoxic T lymphocytes (CTL) and T helper (Th) lymphocytes against the tumor-associated antigen HER2 using autologous dendritic cells (DC). Human dendritic progenitor cells were transduced with a retrovirus encoding the HER2 gene and then further matured into CD83+ DC. HER2-expressing DC were used as antigen presenting cells for stimulating autologous T cells in vitro. HER2-transduced DC elicited HER2-specific CD8+ CTL that lysed HER2-overexpressing tumor cells in context of distinct HLA class I Simultaneously, retrovirally transduced DC induced HER2specific CD4+ Th1 cells that released IFN-gamma upon stimulation with DC pulsed with the recombinant protein of HER2. This method of stimulating HER2-specific CD8+ and CD4+ T cells was successfully implemented for generating HER2-specific CTL and Th1 clones from a patient with HER2-overexpressing breast cancer. These data indicate that retrovirally transduced DC expressing the HER2 molecule present multiple pentide epitopes and subsequently elicit HER2-specific CTL and Th1 cells. The ability to generate HER2-specific, HLA-restricted CTL and Th1 clones facilitates the development of adoptive T cell therapy for patients with HER2-overexpressing tumors.