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Lymphoma: How the tumor escapes the immune response

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Natural killer cells of the immune system can fend off malignant lymphoma cells and thus are considered a promising therapeutic approach. However, in the direct vicinity of the tumor they lose their effect. Scientists of Helmholtz Zentrum München have now elucidated which mechanisms block the natural killer cells and how this blockade could be lifted. The results were recently published in the *European Journal of Immunology*.

Natural killer cells (NK cells) are part of the immune system and provide an innate immunity against exogenous and altered endogenous structures. This also appears to apply to tumor cells, against which the body could develop immunity as it does against pathogens, e.g. against viruses. Tumors of the lymph nodes, called lymphomas, are malignant neoplasms that originate from the B cells or T cells of the lymphatic system. B cell lymphomas are very difficult to treat - which is why innovative approaches to therapy are needed. Earlier studies have shown that NK cells have the potential to attack B lymphoma cells and are therefore considered a possible approach to new treatment strategies. In the living organism, however, tumor control by NK cells has been found to be clearly limited.

NK cells become functionally impaired in the tumor microenvironment

In their experiments, the team led by Prof. Dr. Ralph Mocikat of the

Institute of Molecular Immunology (IMI) at Helmholtz Zentrum München, found that the NK cells in the immediate vicinity of the tumor showed reduced function. If the cells were placed in a normal environment, their function could be restored within a few hours. This suggests that the factors responsible for the inactivation of the NK cells derive from the tumor itself.

An inflammatory cytokine inactivates NK cells - altered surface molecules block immune activation

The scientists engaged in the research project identified two important tumor-specific factors that are associated with impaired NK cell function. First, a specific inflammatory cytokine (IL-10) is indirectly involved in the inactivation of NK cells. Second, the tumor cells develop protective mechanisms against the NK cells. Thus, the research group showed that specific surface molecules of the tumor cells (NKG2D ligands) which NK cells could bind are down-regulated. Consequently, the NK cells lack an important activation mechanism and are no longer able to carry out cytotoxic activity. Despite the inhibitory strategies of the tumor cells, at an early stage the NK cells produce the cytokine interferon-gamma (IFN-γ), the scientists reported. IFN-γ is essential to activate further immune responses that support the fight against the tumor.

Immunotherapy possible using NK cells - with optimization potential

"Our results show that the transfer of NK cells is a possible strategic option to treat B cell lymphoma. According to our findings, this therapeutic approach can be optimized when transferred NK cells are already activated in vitro prior to their injection, thus bypassing the missing activation potential in the tumor microenvironment. An

additional injection of IFN-γ or of antibodies against IL-10 could further support the immune activity," said study leader Mocikat.

More information: Belting et al. (2015), Critical role of the NKG2D receptor for NK cell-mediated control and immune escape of B-cell lymphoma. *European Journal of Immunology*,
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