Healthcare industry BW

Glycosylation pattern as potential target for intervention

Tumours develop sophisticated strategies to escape the immune defence. One of these strategies is the modification of the cells' sugar coat. Specific immune cell receptors bind to these sugars, thereby preventing the tumour cell from being discovered by the immune system. Medics from the University of Tübingen are investigating the mechanisms involved and are looking for therapeutic targets.

All body cells are glycosylated; this means that sugar structures are attached to their surface. Lectins, i.e. proteins specialized in recognising and binding to sugar structures, can dock to these sugars.

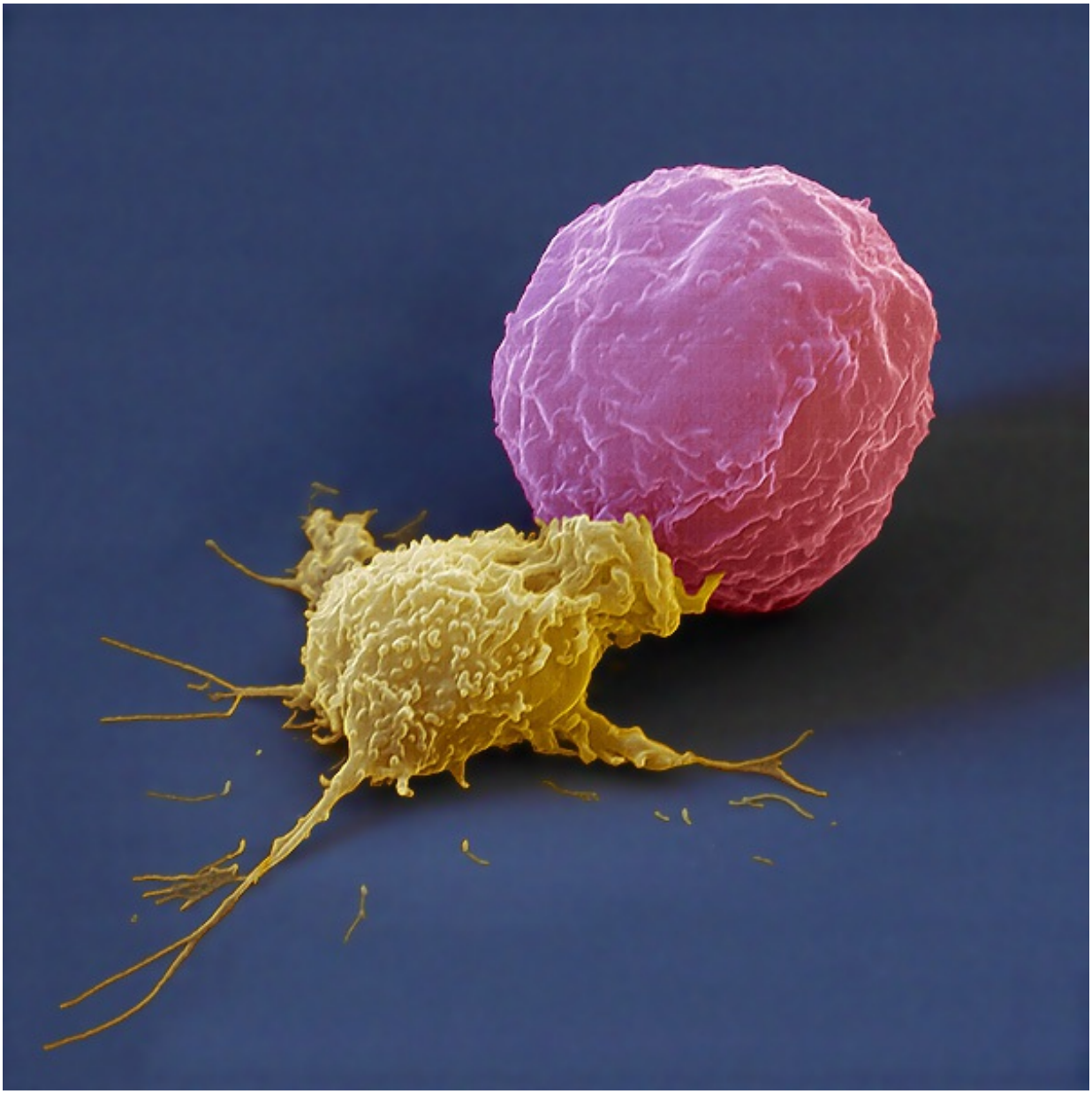
Dr. Ingo Müller from the Clinic for Children's and Youth Medicine at Tübingen University Hospital (Photo: private)

Normally, such mechanisms are used to mediate cellular communication and transport processes, and they are also used in immune system cells. However, cancer cells use the mechanisms to outwit the immune defence. The surface of tumour cells has an unusual glycosylation pattern. “The modification in the glycosylation pattern is one of the first things that happens when cells degenerate; this shows how important the sugar coat is,” said Dr. Ingo Müller of the Tübingen University Clinic for Children’s and Youth Medicine.

Müller is investigating the processes that happen on neuroblastoma cells. Neuroblastomas are malignant tumours that occur predominantly in the adrenal glands. They are the second most frequent type of tumour in children and the most frequent type of tumour outside the nervous system. “It is very important to find a treatment, not only because of the unfavourable prognosis of this type of tumour; the survival rate is only 40 to 60 percent,” said Müller. Together with five colleagues, Müller is investigating how the sugar coat of neuroblastoma cells interacts with immune cells, a project that comes within the scope of the BMBF’s workgroup contest.

Examining the interaction of sugar structures in the mouse model

Müller’s team is using a particular mouse model, which enables the scientists for the first time ever to examine the interaction between neuroblastoma cells and human immune cells in the living system. Müller used to work in Memphis, USA, in the department of Prof. Dr. Rupert Handgretinger who was involved in developing this mouse model before bringing it to Tübingen. The mouse model is so special because the mice are transplanted with human haematopoietic stem cells that produce human immune cells. “Our mouse model enables us to regenerate all the cells in the human immune system. The model has mainly been used to study the development of the immune system, but will now be used to investigate the immunological interactions with the sugar coats of neuroblastoma cells,” explains Müller.



A natural killer cell (NK cell, yellow) of the immune cell attacking a cancer cell (red). (Photo: (Photo: © eye of science, sample: Prof. Dr. Rupert Handgretinger)

The sugar structures on neuroblastoma cells consist mainly of sialic acid, very acid sugar chains bound to specific membrane lipids. The most frequent complex is GD2, a disialoganglioside with sugar residues that carry two sialic acids. GD2 almost exclusively occurs in neuroblastoma cells. This is why the molecule is not only a suitable marker for this type of tumour, but also a potential target for specific therapies. The physicians from Tübingen have already used GD2 in immunotherapies in which antibodies against GD2 were developed that bind to the molecule and present it to the cell destruction machinery of the immune system.

Antibodies against sugar structures have a therapeutic effect

"Antibody-induced cytotoxic reactions occur both in cell cultures and when they are given to patients. We are now hoping to modify the antibodies to make them even more effective. Research into the structure of GD2 and its binding partners will provide us with further therapeutic strategies," said Müller. Two groups of lectins - siglecs (sialic acid-binding proteins) and galectins - have already been identified as important binding partners.

Siglecs are, amongst other places, found on the surface of natural killer cells (NK-cells) of the immune system. An immune reaction is prevented if they bind to the sialic acid residues of the cancer cells. The mechanism is still largely unknown. Müller and his team are now investigating the structures and interactions of siglecs. "The structure of siglec-7 is already known. Working together with Prof. Dr. Thilo Stehle, we now hope to co-crystallize the molecule with GD2 in order to obtain the structure of the entire complex," said Müller.

Research on the sugar structures on cancer cells is still in its infancy

Once an exact image is available, Müller is hoping to find suitable targets that prevent harmful processes. "The knowledge of the exact structure of the sugar-siglec complex will potentially enable us to develop specific inhibitors, i.e. small molecules that bind to the siglecs and prevent sialic acids from binding. Normally, such small molecules can be well tolerated. Metabolic problems will most likely not occur. And allergies to such small molecules are not known," said Müller.

In summary, research on tumour glycobiology is still in its infancy, and many relationships still have to be clarified. For example, sialic acids are also found on the surface of certain leukaemia cells. "T-cell leukaemias have sialic acids, but not so childhood B-cell leukaemias. But the prognosis for patients with T-cell leukaemia is worse than that for patients with B-cell leukaemia," said Müller explaining that further research is required to elucidate the mechanisms involved.

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