GERMAN CANCER RESEARCH CENTER
IN THE HELMHOLTZ ASSOCIATION

50 Years – Research for
A Life Without Cancer

No. 19 May 30, 2016 (Sel)

Natural Killer cells contain powerful toxin against tumors

Scientists at the University Hospital and the DKFZ in Heidelberg have discovered that a protein from immune cells paralyzes the energy supply in tumor cells. The German Society of Pathology has awarded them with the Novartis Prize. The scientists have now published their findings in Nature Communications.

This potentially new agent was discovered in so-called natural killer cells by scientists of the Clinical Cooperation Unit DKFZ and Heidelberg University Hospital under Dr. Georg Gdynia and Professor Wilfried Roth, who now works at the University Hospital in Mainz. These natural killer cells “patrol” the body. When they encounter tumor cells, provided they recognize them as such, they inject them with a lethal protein cocktail. In this toxic mix, pathologists have identified the High Mobility Group Box 1 (HMGB1) protein as a highly effective natural agent against cancer: It paralyzes a mechanism of energy production that is generally used by tumor cells, but not by healthy body cells. This type of 'cell murder' by the immune system has so far been unknown. Together with colleagues from the Heidelberg Institute for Theoretical Studies (HITS) and the Inorganic-Chemical Institute at Heidelberg University, they have now published their results in *Nature Communications.*
The killer cells carry a readily available protein mix in small bubbles (granula) which kills tumor cells within a few minutes. And this property makes it an interesting object for cancer research. The composition of this toxic cocktail has already been investigated. “However, so far only entirely different mechanisms have been described, for example the fact that it attracts other immune cells and helps them mature“, explains Gdynia, “but only now has it shown its potential as a cell toxin“.

In animal testing, tumors shrink or die completely

After the Heidelberg scientists managed to filter the key protein out of the mix, tests with tumor cells showed that it is capable of a lot more than just enhancing the immune response: it interrupts an important metabolic pathway which helps tumor cells to break down the sugar glucose and turn it into energy. As a result, the entire molecular process system collapses. In order to test the effect on whole tumors, the group produced large amounts of the HMGB1-protein by prompting killer cells from healthy blood donors to release the protein. In the mice that had been treated with HMGB1, colorectal tumors shrunk and some even disappeared completely.
"Immunotherapies normally aim to enhance the immune system so it can recognize cancer cells better and fight them more effectively. A therapy with HMGB1 would carry the advantage that it uses the weapons of the natural immune system without depending on its functionality, and still manages to target cancer cells in a very selective manner," explains Gdynia. Obtaining the protein is rather difficult, as you have to catch exactly the right one: "The effectiveness of HMGB1 has been intangible because there are countless varieties. The difference between them is minimal but they each carry a different function“, the pathologist continues.
Only the HMGB1 from the granula of killer cells is able to kill cancer cells, whilst HMGB1 taken out of the cell nucleus is not. Human HMGB1 produced with the help of bacteria also fails to show an equally strong result. The group has registered for patent approval both their scientific technique for obtaining the protein from killer cells, and the new therapy concept. The aim is to develop a new form of therapy for cancer patients.

Georg Gdynia was awarded the Novartis Prize for his discovery by the German Society of Pathology (DGP) at their Centenary Annual Meeting in Berlin in May 2016. He shares the prize, worth 10,000 Euros, in equal parts with the biochemist Dr. Jan Pencik from the Medical University of Vienna.
In the meantime, Gdynia and his colleagues around Adelheid Cerwenka at DKFZ have published further results in "Molecular & Cellular Oncology". Here, they report that HMGB1 can also kill particularly aggressive cancer cells that are resistant to radiation and chemotherapy. These tumor cells are often only loosely connected to the blood supply, they need hardly any oxygen to survive and cope with the toughest conditions. The group is currently developing the world's first test for oncologists to determine the rate of these highly aggressive cells in their patients' tumors. This information will allow doctors to more accurately anticipate how likely the cancer is to grow back, or how well it responds to standard medication, and choose the adequate therapy accordingly. Further plans for this test called “Energetic Fingerprinting”(EnFin) include launching a start-up company in 2017, part-financed by 700,000 Euro from "eXist-Forschungstransfer", an initiative by the Federal Ministry of Economics and Technology (BMWi).

An image for this press release is available at:
http://www.dkfz.de/de/presse/pressemitteilungen/2016/bilder/HMGB1.jpg
BU: HMGB1 positive (red color indication) immune cells infiltrate a colon carcinoma.

An image of Dr. Georg Gdynia is available at:
http://www.dkfz.de/de/presse/pressemitteilungen/2016/bilder/gdynia.jpg
BU: Dr. Georg Gdynia, Clinical Cooperation Unit for Molecular Tumor Pathology DKFZ and Heidelberg University Hospital; Image: Universitätsklinikum Heidelberg

Literature:
Gdynia G, Sauer SW, Kopitz J, Fuchs D, Duglova K, Ruppert T, Miller M, Pahl J, Cerwenka A, Enders M, Mairbäurl H, Kamiński MM, Penzel R, Zhang C, Fuller JC, Wade RC, Benner A, Chang-Claude J, Brenner H, Hoffmeister M, Zentgraf H,Schirmacher P, Roth W. The HMGB1 protein induces a metabolic type of tumour cell death by blocking aerobic respiration. Nat Commun. 2016 Mar 7;7:10764. doi:10.1038/ncomms10764. PubMed PMID: 26948869; PubMed Central PMCID: PMC4786644.
Adelheid Cerwenka , Jürgen Kopitz , Peter Schirmacher , Wilfried Roth , Georg Gdynia. HMGB1: the metabolic weapon in the arsenal of NK cells. Molecular & Cellular Oncology. http://dx.doi.org/10.1080/23723556.2016.1175538

Contact:

Dr. Stefanie Seltmann
Head of Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2854

F: +49 6221 42 2968
presse@dkfz.de

Dr. Sibylle Kohlstädt
Press and Public Relations
German Cancer Research Center
Im Neuenheimer Feld 280
D-69120 Heidelberg
T: +49 6221 42 2843
F: +49 6221 42 2968
Email: presse@dkfz.de