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Malaria Drug Artesunate Activates Lysosomal Cell Death in Cancer Cells

Heidelberg scientists have investigated cellular processes in killing breast cancer cells.

Artemisinin – a substance obtained from a medicinal plant used for the treatment of malaria may potentially be used also for cancer treatment. Scientists of BioQuant Center of Heidelberg University and the German Cancer Research Center (Deutsches Krebsforschungszentrum, DKFZ) have investigated cellular processes in killing breast cancer cells using artesunate, an artemisinin derivative. They were able to show that membrane-bound cell organelles known as lysosomes and reactive iron contained therein play a key role in artesunate-induced cell death of cancer cells. Their research results were published in the *Journal of Biological Chemistry*.

Extracts of the medicinal plant *Artemisia annua* (annual wormwood) have been used in traditional Chinese medicine for over two thousand years. In the 1970s, the active substance artemisinin was identified and clinically characterized as an effective antimalarial agent. Today, artemisinins are used worldwide for malaria treatment. One of its derivatives is artesunate, which like artemisinin unfolds its cytotoxic effect through chemical reaction with iron. In the process, reactive oxygen species, commonly known as free oxygen radicals, are produced. In malaria parasites, the cytotoxicity of artemisinin originates from the food vacuole, which contains high levels of redox-active iron formed as a result of the breakdown of host hemoglobin.

Analogous to the food vacuoles of the malaria parasite, the Heidelberg group studied the role of lysosomes in artesunate-induced programmed cell death in breast cancer cells. Lysosomes are membrane-bound eukaryotic cell organelles which use specific enzymes to break down cellular components. In addition, like the food vacuole of malaria parasites, they contain high levels of redox-active iron. This lysosomal iron was identified by the investigators as the key starting point of cell death induced by artesunate in breast cancer cells. The research group “Systems Biology of Cell Death Mechanisms” headed by Dr. Nathan Brady found out that blockage of reactive iron in the lysosomes protects cancer cells, while, on the other hand, an increase of lysosomal iron levels enhances the cytotoxic effect of artesunate on cancer cells.

Dr. Anne Hamacher-Brady, scientist in the research group “Integrative Bioinformatics and Systems Biology“ headed by Prof. Dr. Roland Eils explains that intact lysosomes are required for the cell death signal to be passed on to the mitochondria. Mitochondria, normally known as the powerhouses of the cell, frequently play a role in programmed cell death, or apoptosis, by releasing what are called pro-apoptotic molecules. In artesunate-induced cell death, this transformation of mitochondria into killer organelles happens depending on lysosomal iron. The scientists were also able to show that artesunate, through its influence on the spatial distribution of cellular components, blocks particular processes which normally support survival and spread of cancer cells. This includes, among others, the process of autophagy in which a cell uses its lysosomal machinery to break down own components in order to recycle vital macromolecules in situations of restricted nutrient supply such as inside a tumor.

As the Heidelberg researchers report, cell death through artesunate was triggered only in breast cancer cells, not in “healthy” mammary epithelial cell lines. Their hypothesis is that

this selectivity for cancer cells may be caused by the fact that cancer cells have an increased need of iron due to changes in their metabolism. This is the subject of ongoing studies conducted by the two research groups at BioQuant Center. More information is available on the Internet at http://ibios.dkfz.de/tbi under the keyword “Artesunate“.

Original publication:
A. Hamacher-Brady, H.A. Stein, S. Turschner, I. Toegel, R. Mora, N. Jennewein, T. Efferth, R. Eils, N.R. Brady: Artesunate activates mitochondrial apoptosis in breast cancer cells via iron-catalysed lysosomal reactive oxygen species production. J Biol Chem. 2011 Feb 25; 286(8): 6587-6601, DOI: 10.1074/jbc.M110.210047.

Contact:
Dr. Nathan Brady
DKFZ and University of Heidelberg
BioQuant-Zentrum, Phone ++49 (0)6221 54-51322
nathan.brady@bioquant.uni-heidelberg.de

Prof. Dr. Roland Eils
University of Heidelberg and DKFZ
BioQuant-Zentrum, Phone ++49 (0)6221 54-51290
roland.eils@bioquant.uni-heidelberg.de

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