Human immune cells react sensitively to 'stress'

February 2 2012

Scientists working with Professor Bernd Kaina of the Institute of Toxicology at the Medical Center of Johannes Gutenberg University Mainz have demonstrated for the first time that certain cells circulating in human blood – so-called monocytes – are extremely sensitive to reactive oxygen species (ROS).

They were also able to clarify the reason for this: ROS are aggressive forms of oxygen that are generated during states of "oxidative stress" and play a significant role in various diseases. However, ROS are also naturally produced by cells of the immune system, in particular by macrophages, in response to exposure to pathogens. Macrophages are, similar to dendritic cells, generated by monocytes, which happens when monocytes leave the blood stream and enter the tissue. The scientists show that both macrophages and dendritic cells are resistant to ROS, as opposed to their precursor cells, the monocytes. The Mainz team attributes this hypersensitivity of monocytes to multiple defects in DNA repair that are apparent in these cells. They assume that a sophisticated mechanism for regulating the immune response and preventing excessive ROS production is behind this phenomenon, which was observed for the very first time. Their work has been published in the leading scientific journal *Proceedings of the National Academy of Sciences*.

It is generally known that one of the undesirable effects of ionizing radiation and drugs used to treat cancer is an impairment of the immune system, which ceases to function properly. However, it is still unclear which immune system cells respond most sensitively following radio-

and chemotherapy, and which cells are resistant. "This is the question we addressed in our current research project," explains Professor Dr. Bernd Kaina, Director of the Institute of Toxicology at the University Medical Center in Mainz. "We were able to demonstrate that human monocytes are hypersensitive to reactive oxygen species (ROS), while macrophages and dendritic cells derived from monocytes by cytokine maturation are resistant." The scientists observed this extreme sensitivity of monocytes after exposure to radiation, chemicals, and even oxidized low-density lipoprotein (oxLDL), which plays a role in atherosclerosis. All of the above resulted in the formation of intracellular ROS, which damages the DNA and leads to cell death or even malignant transformation. Specific immune system cells, particularly the macrophages, produce ROS in response to an invasion of the body by pathogens. Ideally, production of ROS should cease once the pathogens have been eliminated. There also need to be limitations on the quantity of ROS produced, as these can damage healthy cells in inflamed tissue as well. In fact, chronic infections, in which ROS are continuously being produced, are frequently linked to an increased susceptibility to cancer.

Why do monocytes react so sensitively to ROS? Kaina's team has successfully determined the cause of the hypersensitivity of monocytes to oxidative stress: The monocytes were unable to repair DNA following ROS-induced damage to their genetic substance. This is because these cells produce very low levels of certain important repair proteins called XRCC1, ligase III, PARP-1, and DNA-PK in medical jargon. "Monocytes are in fact defective as far as two important DNA repair systems are concerned, i.e. base excision repair and DNA double-strand break repair," explains Kaina. "Thus far, a general repair defect of this nature has been observed neither in the cells of the human body nor in experimental in vitro systems."

Professor Kaina assumes that the repair defect in monocytes plays an important role in the regulation of the immune response: To prevent

excessive production of ROS by macrophages in the inflamed tissue and an overactivation of the immune response, monocytes, as precursor cells of the ROS-producing macrophages, undergo increased and selective destruction due to their extreme sensitivity to ROS. In turn, fewer monocytes mean fewer macrophages and consequently lower levels of ROS – all in all a sophisticated way of regulating the monocyte/macrophage/dendritic cell system. It is clear that this has potential clinical implications: In the case of chronic inflammatory diseases in particular, the body is in a state of imbalance and excessive amounts of ROS are produced, which results in damage to the genetic substance of the healthy cells and is a contributing factor to the onset of cancer. It is possible that this vicious circle could be interrupted by the selective elimination of monocytes in the inflamed tissue.

Provided by Johannes Gutenberg Universitaet Mainz