

Memories of origin

The endothelial cells store information in the state in which they were extracted from the donor

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Cells have memory. Possibly not all cells have memory, but some are able to remember, at a later point, the conditions of the organism and the environment from which they were extracted. This ability to retain and transmit information to the descendants has not been observed, as one might expect, in neurons, the brain cells that transport information in the form of electric signals from one point to the other within the organism and store this information in the brain. A team led by the pharmacologist Regina Pekelmann Markus identified cell memory in the endothelium, which is the layer of cells that lines the interior surface of blood vessels.

Currently observed in rats, this form of remembering, described in an article published in November in *PLoS ONE* journal, is expected to arouse medical interest because it may represent a means to influence organ transplants and to develop tissues in the lab that could substitute natural tissues. "If these findings are confirmed in human beings, it will become necessary to pay attention to cell memory in order to obtain more homogeneous tissue cultures and reduce the risk of rejection in the case of transplants," says the researcher from the University of São Paulo (USP).

The discovery of cell memory occurred quite unexpectedly. At the Chro-

nopharmacology Laboratory of USP's Biosciences Institute (IB), the group led by Regina was cultivating endothelial cells of healthy rats in acrylic recipients. The researchers were also cultivating, in the same manner, endothelial cells of animals that underwent a test simulating an acute infection, which was triggered by the injection of lipopolysaccharide (LPS) molecules from the bacteria's cell walls. After reproducing both groups of cells *in vitro* for nearly three weeks, the researchers observed that the second set of cells behaved just like their great-great-grandparents.

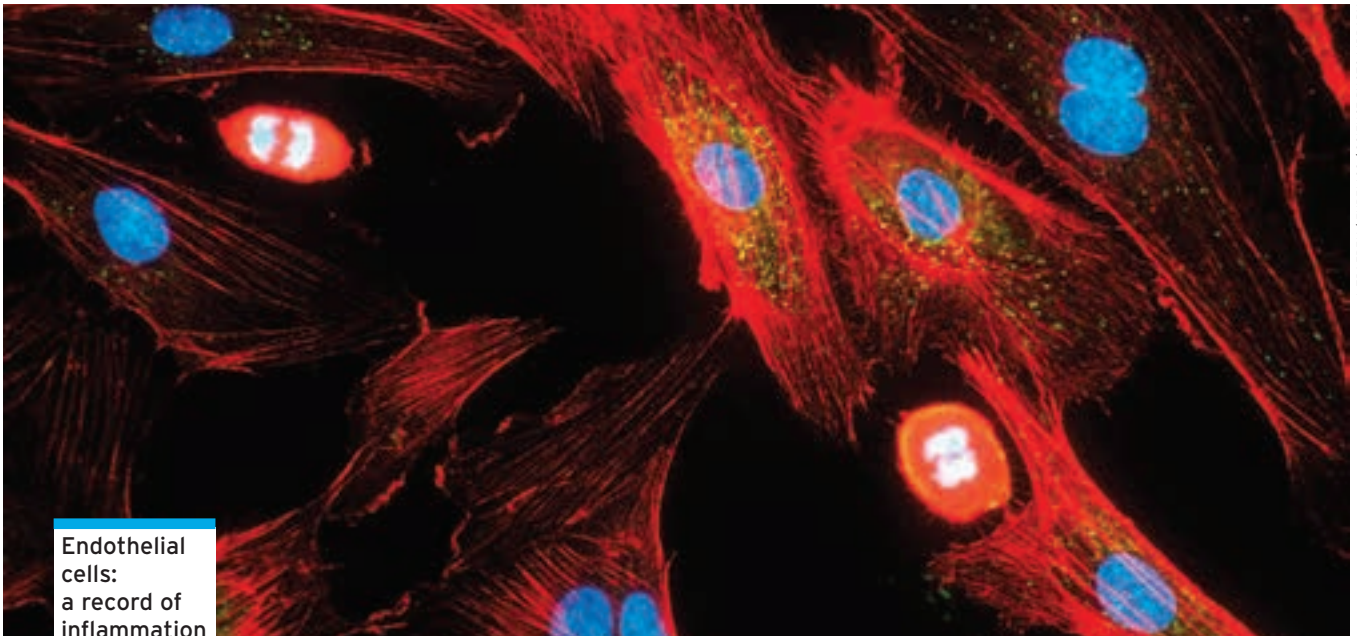
The cells extracted from rodents with the inflammation reproduced the physiological processes that occur in the endothelium of an injured part of the body: they attracted and retained the defense cells, especially the neutrophils, which are the most abundant immune cells in the organism and one of the first cell types to reach the inflamed region. The endothelial cells that stemmed from the cells removed from the rats without inflammation behaved as if they were in a healthy environment.

If this phenomenon occurs in rats, the experimental model of various diseases, it is possible that it occurs in human beings as well because the physiology and structure of human organs and tissues and those of rodents are similar. If cell memory is identified in human beings, this memory might

explain, at least in part, the rejection of transplanted organs. Immediately after a heart attack, for example, the endothelium cells produce and expose molecules that attract neutrophils to their surface. Normally dragged at high speed by the blood stream, the neutrophils adhere to the endothelial cells that slow them down until they stop.

Next, the neutrophils squeeze through the endothelium cells, cross the blood vessel and move through the tissues until they reach the damaged cells. This process, which is the same process that occurs in bacterial infections, causes swelling, temperature increases, and pain in the affected area. According to Regina, this process also leaves a molecular scar. This is why it is possible that a cell that is removed from a person who had a heart attack might carry the memory of this inflammation in its cells, thus increasing the risk of rejection. "This is an important concept and, in principle, might affect the result of transplants; however, we still don't know if this actually happens," says immunologist Mauro Teixeira of the Federal University of Minas Gerais.

Salvatore Cuzzocrea, a researcher at the University of Messina in Italy, is a specialist in inflammation. He says that "the idea of monitoring the activation state of the donor's cells seems like a good beginning to reduce the risk of rejection. We must keep in mind that



**Endothelial cells:
a record of
inflammation**

damage to the endothelium is the main cause of unsuccessful transplants.”

The suspicion that cells might retain the memory of a state for long periods of time first surfaced in 2008. In the laboratory headed by Regina, biologist Eduardo Tamura, who was enrolled in the doctorate program at the time, was also working on the standardization of inflammation tests and was trying to discover whether the production of a compound - nitrous oxide (NO), synthesized by the endothelial cells during inflammation and which relaxes the

blood vessels by increasing the flow of blood to the injured area – varied during the day. Some years before, Regina and pharmacologist Cristiane Lopes had demonstrated that the intensity of the inflammation swings in 24-hour cycles; the intensity is higher during the day and milder at night. The swinging is controlled by the melatonin hormone, the production of which increases after sunset. Synthesized by the pineal gland, which is located in the brain, melatonin tells the organism that it is dark outside and that its cells have to execute the tasks they normally carry out at night.

Physiologist Celina Lotufo, a researcher at the Federal University of Uberlândia and a former student of Regina, verified that melatonin inhibits inflammation because it acts on the endothelium: melatonin prevents the neutrophils from adhering to the endothelial cells and beginning the inflammatory response. However, the researchers still had to detail this interaction from the biochemical standpoint. Tamura noticed that the melatonin blocked the production of nitrous oxide, reducing the relaxation of the vessels and the arrival of blood and neutrophils to the site of the injury.

In 2008, because of a winter course organized by the Department of Physiology of the IB, Tamura changed the time during which he prepared the rodents for the experiments and was surprised by the result. Instead of in-

jecting the inflammatory compound during the day, he started injecting it at night. When comparing the responses, he noticed that the animals that were injected with the LPS at night produced less nitrous oxide, a sign of less intense inflammation. The anti-inflammatory effect, he noticed, resulted from the action of melatonin, which reduces the production of nitrous oxide by the neutrophils and by the endothelial cells.

When cultivating the endothelial cells for longer periods of time, Tamura and biologists Marina Marçola and Pedro Fernandes noticed that they stored the memory of the health conditions of the rats for up to 18 days; in fact, the cells extracted from rats with inflammation behaved as if they were still living in an inflamed organism.

Under certain conditions, this memory was deleted by melatonin. “When melatonin was given to the animal before the inflammation was stimulated, it prevented this kind of recollection,” says Regina. “But we still don’t know whether the action of this hormone on the endothelial cells is direct or indirect or whether it is possible to revert the memory of the *in vitro* inflammation.” ■

Scientific article

TAMURA, E. K. *et al.* Long-lasting priming of endothelial cells by plasma melatonin levels. **PLoS ONE**, v. 5 (11), 12 Nov. 2010.

THE PROJECTS

1. *Pineal gland and melatonin - timing mechanism of neural responses and inflammatory process - n° 2002/02957-6*
2. *Immune-pineal axis - endocrine and paracrine production of melatonin in conditions of injury - n° 2007/07871-6*

TYPE

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COORDINATOR

1 and 2. Regina Pekelmann Markus - IB/USP

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