Study can orient use of melatonin in the treatment of breast cancer

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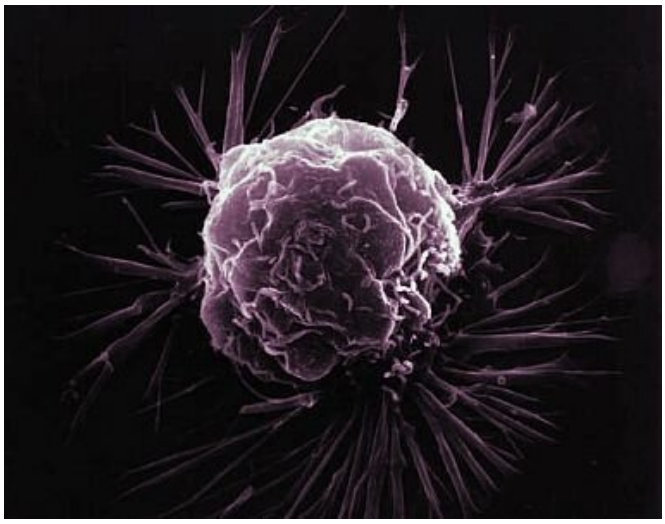

In an article published in the Journal of Pineal Research, researchers at São Paulo State University and collaborators describe a set of genes potentially regulated by the “sleep hormone” in some types of tumor (close-up of a breast cancer cell) . Credit: NCI/NIH

A Brazilian study published in the *Journal of Pineal Research* describes a group of genes potentially regulated by the hormone melatonin in some types of cancer, especially breast cancer. According to the authors, the results can be used to guide future personalized therapies for the disease.

"Certain types of tumor appear to correlate directly with the amount of melatonin produced by cells. It's essential to understand how the hormone influences molecular signaling at the genetic level as a guideline for personalized therapies based on melatonin," Luiz Gustavo Chuffa, a professor at São Paulo State University's Botucatu Institute of Biosciences (IBB-UNESP), told Agência FAPESP.

The study was supported by FAPESP and conducted in collaboration with researchers at the University of North Paraná (UENP) and São José do Rio Preto Medical School (FAMERP) in Brazil and the University of Texas Health Science Center at San Antonio in the United States.

Known as the "sleep hormone" because its functions include regulating the sleep-wake cycle, melatonin has been shown to have anti-tumor properties in laboratory trials. Evidence presented in the scientific literature suggests that low levels of melatonin are associated with a heightened risk of cancer. A possible explanation is that the hormone contributes to the modulation of gene expression and may intensify the activity of tumor suppressor genes, for example.

"Most tumor cells have low levels of melatonin, but laboratory trials have shown that treatment with the hormone increases tumor cell death and reduces tumor cell proliferation, both of which are important to avoid progression of the cancer and metastasis," Chuffa said. "Ongoing clinical trials are evaluating the use of melatonin to treat cancer. Specific therapies for the different subtypes of breast cancer already exist, and some patients will probably respond well to alternative treatments based on melatonin, while others may not."

In search of target genes

To identify molecular markers that serve as guides for cancer treatment, the researchers first conducted a study based on meta-analysis to find out how melatonin regulates microRNA expression in breast, head and neck, liver, stomach, prostate, central nervous system, and colorectal cancer.

Meta-analysis entails a systematic review of the literature using statistical methods to integrate the results of published research on the same subject. MicroRNAs are small RNA molecules that do not encode proteins but perform a regulatory function in the genome, controlling gene expression and hence several cellular processes.

"In this first stage, we found 14 quite recent studies that associated melatonin with altered microRNA expression. For the seven cancers on which we focused, we found 46 microRNAs with altered expression," Chuffa said.

Next, the researchers used bioinformatics to identify pathways associated with the hormone's action on tumor cells, basing their analysis on the association between these microRNAs and their regulatory targets. Regulatory and molecular networks were generated and analyzed in collaboration with researchers Robson Francisco Carvalho, Luis Antonio Justulin, and Sarah Santiloni.

"When we cross-referenced the information with The Cancer Genome Atlas [TCGA], a public database, we identified the target genes for these 46 microRNAs with altered expression," Chuffa said.

As a result, they were able to understand how melatonin works in several cellular signaling pathways. "These genes targeted by melatonin relate to important biological processes in cancer, such as cell cycle regulation, cell death, and cell migration and senescence," he explained. "Melatonin appears to act more strongly on breast, oral, and stomach cancer. Prostate and colorectal tumors, as well as glioblastoma, showed few changes induced by the microRNAs concerned."

Breast cancer was associated with the most genes and microRNAs in this first stage of the study, so the researchers compared the target genes for the microRNAs concerned with the data obtained by RNA-seq analysis of breast tumors in mice treated with melatonin.

RNA-seq uses next-generation sequencing technology to study the expression of several genes at the same time and hence to obtain the entire transcriptome, i.e. the complete set of RNA molecules expressed in a tissue.

These analyses were performed in partnership with FAMERP researchers Débora Aparecida Pires de Campos Zuccari and Bruna Victorasso Jardim-Perassi.

"In the animals treated with 40 milligrams of melatonin, there was an enrichment of signaling pathways related to the immune system and apoptosis, and a reduction of pathways associated with tumor aggressiveness and metastasis," Chuffa said.

The group also investigated certain proteins (transcription factors and kinases) that are active in such processes as transcription and the cellular cycle. "The goal of this part of the study was to find common targets in cellular processes and the breast cancer public database," he said.

According to Chuffa, genes regulated by melatonin in breast cancer are potential targets for the treatment of the disease. "Melatonin is a multitasking molecule and acts on various cellular substrates, so we're now taking the study deeper to find out how the hormone influences microRNA expression and hence the regulation of the cellular mechanisms identified," he said.

More information: Luiz Gustavo de Almeida Chuffa et al, A meta?analysis of microRNA networks regulated by melatonin in cancer: Portrait of potential candidates for breast cancer treatment, *Journal of Pineal Research* (2020). DOI: 10.1111/jpi.12693

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