Study identifies cancer patients most likely to develop cachexia

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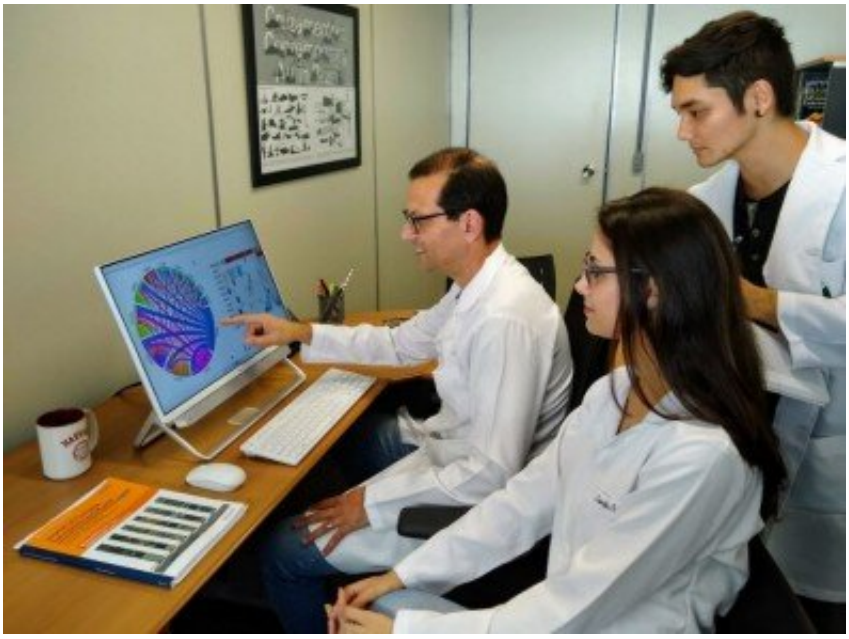

Robson Francisco Carvalho and his team at IBB-UNESP established a gene expression profile associated with cachexia. Credit: Robson Francisco Carvalho

It is estimated that as many as 80% of advanced-stage cancer patients may develop cachexia, a potentially fatal metabolic syndrome characterized by extreme weight loss and muscle wasting, but scientists do not yet fully understand why it is more frequently associated with certain kinds of tumor than others, or why not all cancer patients develop it.

Tumor genetics could provide an answer. Researchers at São Paulo State University (UNESP) in Brazil analyzed 12 types of cancer and identified patterns of tumor protein secretion that correlated with the prevalence of cachexia and average weight loss for each type.

The study was supported by São Paulo Research Foundation—FAPESP. The principal investigator was Robson Francisco Carvalho, a professor at UNESP's Botucatu Institute of Biosciences (IBB). Researchers from the University of Southern Denmark and the University of Antioquia's Medical School in Colombia also contributed to the study. The results were published in the *Journal of Cachexia, Sarcopenia and Muscle*.

According to Carvalho, cachexia is most frequent in patients with pancreatic, esophageal, colorectal, stomach and head and neck cancer, and least frequent in patients with breast and prostate cancer.

"Cachexia-inducing factors, mainly deriving from cancer, had already been associated with development of the syndrome, but it was not yet possible to link them to this variation in its prevalence and severity," he said. "In the case of cancer of the pancreas, for example, which correlates closely with cachexia, we found alterations in the expression of 14 out of 25 genes that encode cachexia-inducing factors. In prostate cancer, which does not, we found no change in the expression of any of these 25 genes."

Tumor databases

The findings of the study were based on an analysis of clinical and molecular data from two public tumor databases, The Cancer Genome Atlas (TCGA) and the Genotype-Tissue Expression (GTEx) project. To delineate a specific tumor profile, the researchers used 4,651 samples of 12 types of cancer and compared them with 2,737 samples of normal tissue from the same organs.

Every cell or tissue produces a transcriptome, a set of RNA molecules responsible for "transmitting" the information encoded by the genes, and for guiding protein synthesis. "Based on transcriptome analysis we compared the gene expression profiles of the proteins secreted by tumors and normal tissue," Carvalho explained.

This initial analysis identified new factors that were specific to each type of tumor and could potentially explain variations in the prevalence and severity of cachexia in cancer. Data on all cellular protein-encoding genes came from the Human Protein Atlas. A total of 2,933 human genes associated with proteostasis have been described to date.

After analyzing the genes for their list of proteins, the researchers focused on investigating the genes that encode the 25 growth factors and cytokines known to be cachexia-inducing factors. These include CXCL8, IL1B, LIF, TGFA and IL6, analyzed in a previous study based on blood samples from cachectic patients with pancreatic cancer.

"In this manner we identified major correlations between the expression profiles of cachexia-inducing factors specific to each tumor type and the prevalence of the syndrome and average weight loss in patients with these cancers," Carvalho said.

In pancreatic cancer, for which the patient survival rate is low, average weight loss is 13.7 kilograms (kg). In prostate cancer, which has a high survival rate, average weight loss is less than 2 kg.

"We also identified major correlations between the expression profiles of cachexia-inducing factors for each type of tumor and a worse patient prognosis [lower survival rate]," he noted.

Patients with end-stage (refractory) cachexia are expected to survive for less than three months.

Biomarkers

The genes described in the article have the potential to serve as biomarkers of the risk of developing cachexia, a complex condition whose treatment continues to defy science. "This suggests each type of tumor requires specific treatment against cachexia," Carvalho said. "Knowledge of this profile can help physicians identify patients with an unfavorable prognosis, which influences important decisions about their treatment."

The researchers at IBB-UNESP had previously made a key discovery in this connection. "Last year, while analyzing cachexia in cases of lung cancer, we found that the protein IL8 secreted by the tumor can induce muscle cell atrophy," Carvalho said.

Conducted in collaboration with the Danish research group and with FAPESP's support, the previous study was published in the journal *Cancers*. "Our analysis of secreted protein gene expression in the tumors of patients with lung cancer and low muscularity as assessed by computed tomography also identified a set of molecules that can be used for prognosis prediction," he explained.

Practical application of this knowledge remains a challenge. "Having identified this set of biomarkers of cachexia with significant prognostic value, we may be able in future to develop a panel for assessment of the expression of these genes in tumor tissue," said Paula Paccielli Freire, who conducted the investigation while researching for a Ph.D. at IBB-UNESP.

The researchers are now analyzing the transcriptomes of individual cells in tumors with a high prevalence of cachexia, using a technique known as single-cell RNA sequencing. Transcriptome analysis was possible hitherto only with samples of tumor mass, which contains a complex

mixture of various cell types.

"With the advance of single-cell RNA sequencing, we're now able to identify exactly which cell secretes which cachexia-inducing factor," Carvalho said.

More information: Paula Paccielli Freire et al, The expression landscape of cachexia-inducing factors in human cancers, *Journal of Cachexia, Sarcopenia and Muscle* (2020). DOI: 10.1002/jcsm.12565

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