News Blog

Looking to Ancient Symbionts for New Cancer Therapies

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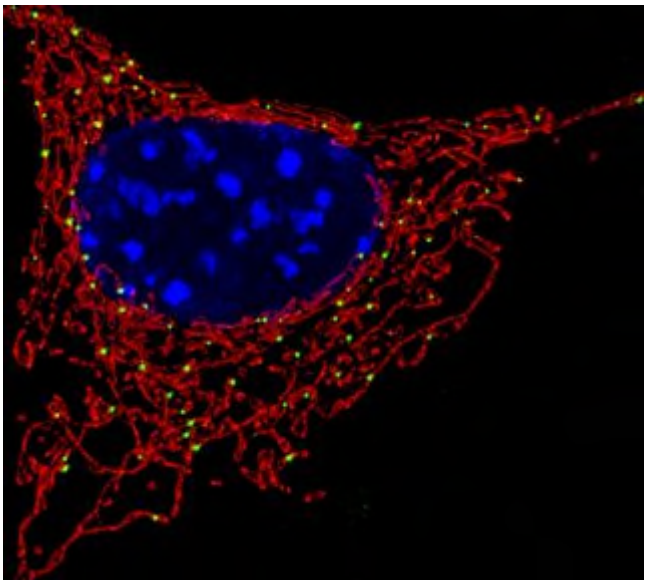

Talk about a eureka moment: **Andrea Facciabene, PhD**, a research assistant professor of Obstetrics and Gynecology, was taking a walk one day on the Penn campus when it hit him: What do we really need to make immunotherapy a reality for everybody? The answer, he thought, was in the mitochondria, the proverbial powerhouses of the cell.

Promising immunotherapy approaches, including cancer vaccines, are only as effective as the tumor-associated antigen (TAA) these vaccines target. (An antigen is any compound or organism that incites the immune system to produce antibodies against it.) But for an effective vaccine, he knew he needed a real TAA as opposed to a synthetic one.

Where would we have more of a chance to find one?
Since mitochondria are ancient simple-cell symbionts living within all higher-order cells, they are the only place inside cells to find extra-nuclear DNA, with a chance to accumulate mutations. The prevailing theory to explain the existence of these cellular subunits is that they arose through a symbiotic relationship between bacteria and other advanced cell-like organisms more than 1.5 billion years ago when life on Earth was starting to take shape.

Mutations in mitochondrial DNA have been found in colorectal, ovarian, breast, urinary bladder, kidney, lung, and pancreatic tumors. Evolution-wise, the 13 proteins that mitochondria make are different from the rest of the proteins of advanced cells. Mutated mitochondria proteins, reasoned Facciabene, would not be “seen” as self-proteins by the body, and therefore an optimal tumor-associated antigen, potentially capable of eliciting an effective anti-tumor immune response.

They were right. Using a renal cell carcinoma cell line, the team showed that these cells harbor tumor-associated mitochondrial antigens (TAMAs for short) that can drive an antitumor immune response. With that, the team produced a mitochondria tumor vaccine that protected animals against kidney cancer development.

“We generated a cellular tumor vaccine by pulsing dendritic cells with mitochondrial proteins from renal carcinoma cells,” Facciabene explained of their recent findings in the *Journal of Immunology*. “The dendritic cells elicit a strong immune response, and our dendritic cell–based renal carcinoma mitochondrial vaccine elicited a cytotoxic T-cell response in mice. It also conferred a durable protection in both prophylactic- and therapeutic-challenged animals with the renal carcinoma cells.”

Potential TAA selection for active or passive immunotherapy strategies such as vaccines must meet a number of criteria. They must be immunogenic, abundantly expressed by tumor cells, not be expressed in normal tissue (so as to limit off-target effects), and, preferably, functionally important for the tumor, so that expression is unlikely to be lost.

Cancer patients bearing mutations in mitochondrial DNA or TAMAs meet all of the criteria of an ideal TAA.

By sequencing the mitochondrial DNA from renal carcinoma cells, the team identified two mutated proteins: COX1 and ND5. Peptide vaccines generated from mitochondrial-encoded COX1, but not from ND5, impaired tumor growth similar to the renal carcinoma mitochondrial vaccine.

From this series of experiments, the team deduced that TAMAs can elicit effective antitumor immune responses. “We feel that this approach has the potential to be a new immunotherapeutic strategy to treat cancer,” Facciabene explained.

After a billion years of living cooperatively in our cells, Facciabene is now poised to use mitochondria to attack human cells gone wrong.

Image courtesy of the National Institute of Child Health and Human Development

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