A class of drugs can harness the power of the body's immune system to fight tumors

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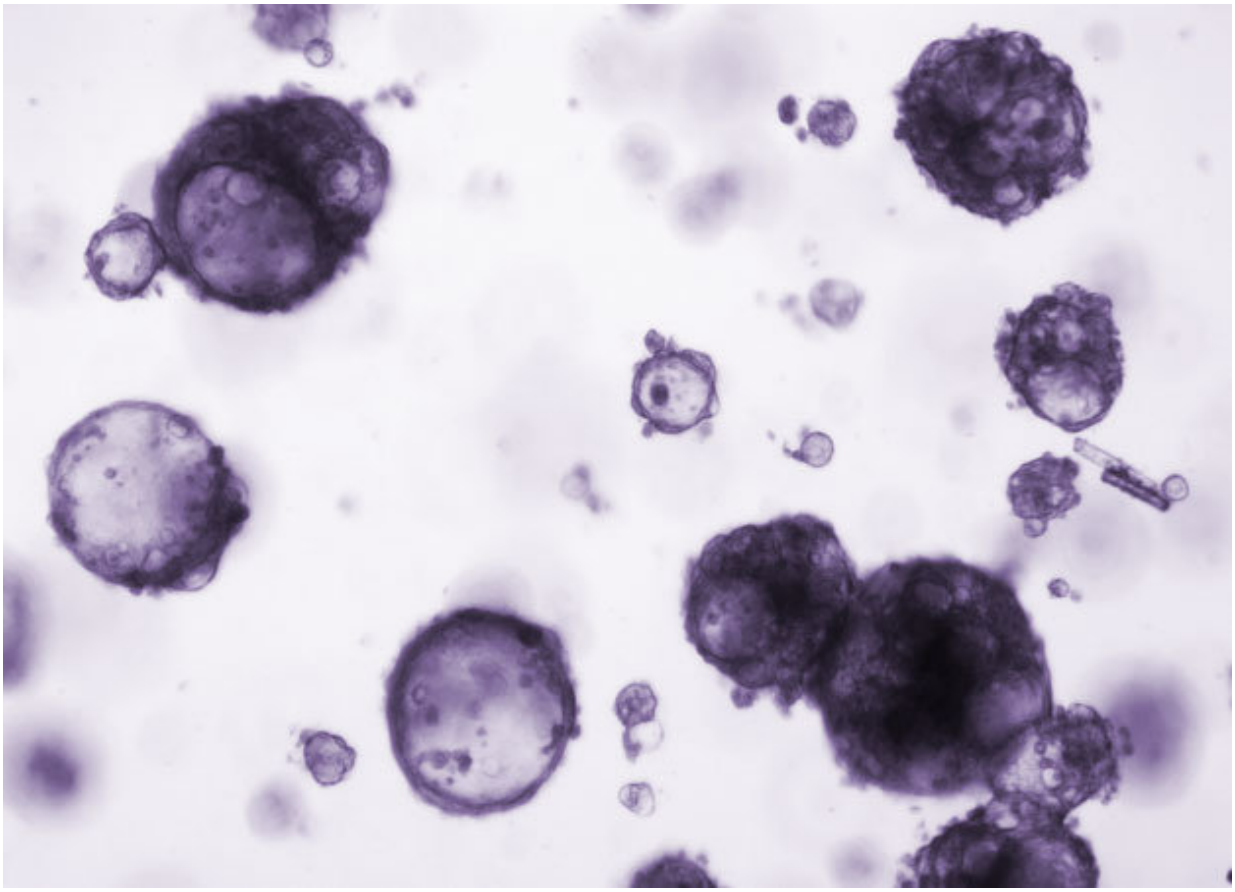

Three-dimensional organoids derived from human cholangiosarcoma tumor cells. Credit: Yoshimasa Saito, Keio University

By stimulating a patient's immune system, a drug already in use to treat a

blood disorder can thwart the growth of a variety of solid tumors, find a team at Keio University.

The drug 5-aza-CdR is currently approved for treating a blood disorder that can lead to leukemia. It inhibits the methylation of DNA, preventing enzymes from chemically modifying genomic DNA. Such modifications can greatly alter the expression of genes that control a variety of critical cellular functions, including cell growth and survival.

Some studies have shown that methylation inhibitors such as 5-aza-CdR could be used to treat other cancers. These effects have generally been attributed to the drugs reactivating tumor-suppressor genes, but the actual mechanism remains poorly understood.

Yoshimasa Saito and his co-workers at Keio University set about figuring out how the drugs work. They began by assessing the effects of 5-aza-CdR on a mouse model of intestinal cancer. The team found that the drug cut the number of tumors that formed by roughly a third and that animals that received the drug tended to have smaller tumors than those that did not.

Having demonstrated that 5-aza-CdR can act on such cancers, the researchers then cultured cells derived from mouse intestinal tumors under conditions that promote the formation of three-dimensional organoids.

"Organoids are budding, cyst-like structures that closely recapitulate the properties of the original tumors," explains Saito, "This makes them a powerful tool for studying how cancers respond to treatment."

The researchers found that 5-aza-CdR strongly inhibited the growth of tumor-derived organoids and were minimally toxic to healthy intestinal cells.

Delving deeper, Saito's team looked at which genes were turned off and on by this treatment and noticed a striking pattern. "Our findings indicated that DNA demethylation suppresses the proliferation of intestinal tumor organoids by inducing an anti-viral response," says Saito. He and his colleagues suggest that the methylation inhibitors are somehow reactivating endogenous retroviruses—ancient viral DNA sequences that have accumulated over evolutionary history and now lie dormant throughout the genome. This initial antiviral response leads to immune activation and the shutting down of tumor proliferation.

"These findings represent a major shift in our understanding of the anti-tumor mechanisms of DNA demethylating agents," says Saito.

The team believes the strategy could be effective for treating other cancers, and it has already obtained promising results with organoids derived from challenging tumors such as cholangiosarcoma and pancreatic cancer. "We are trying to develop a personalized therapy for refractory cancers," says Saito.

More information: Yoshimasa Saito et al. Inhibition of DNA Methylation Suppresses Intestinal Tumor Organoids by Inducing an Anti-Viral Response, *Scientific Reports* (2016). DOI: 10.1038/srep25311

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