

Call of the riled: Stress signal in cancer cells triggers similar response in other cells, aiding tumor growth

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An artist's representation shows how stress signals from cancer cells prompt similar signals in neighboring cells, aiding and abetting tumor growth. Left: To survive in a harsh environment (low oxygen, nutrient deprivation), tumor cells produce constant endoplasmic reticulum (ER) stress response. Center: These ER stress signals are transmitted to nearby macrophages - white blood cells charged with recognizing and removing tumor cells and pathogens. The macrophages react with their own ER stress signals, initiating an inflammation response. Right: The resulting macrophage-amplified inflammation encourages more tumor growth. Credit: UC San Diego School of Medicine

Researchers at the University of California, San Diego School of Medicine say a "stress response" mechanism used by normal cells to cope with harsh or demanding conditions is exploited by cancer cells, which transmit the same stress signal to surrounding cells, triggering an inflammatory response in them that can aid tumor growth.

The findings are reported by Maurizio Zanetti, MD, professor of medicine and director of the Laboratory of Immunology at the UC San Diego Moores Cancer Center, and colleagues, and published in the April

4 early online edition of [Proceedings of the National Academy of Sciences](#).

The endoplasmic reticulum (ER) is the protein-making factory inside all cells. Increased physiological demands or disease conditions can sometimes cause proteins to misfold and accumulate in the ER. Cells typically respond by an ER [stress response](#), which attempts to reset normal ER balance.

For normal cells, the ER stress response is transient. For [tumor cells](#), it's life. Because they exist in an environment that's invariably difficult (their host is always trying to kill them, and oxygen and nutrient deprivation are frequent), tumor cells produce an on-going ER stress response, which helps them not only to survive, but to thrive.

According to Zanetti and colleagues, tumor cells generate "transmissible ER stress." Specifically, they induce bystander cells to issue a similar stress response, most notably nearby [macrophages](#) – a type of white blood cell employed by the body's immune system to recognize and remove pathogens and cellular debris.

Recently, several laboratories, including some at UC San Diego, have underscored the crucial role of inflammation in promoting cancer growth. A consequence of "transmissible ER stress" points to "receiver" macrophages as an important source of inflammation, which serves as an environmental cue for cancer development.

"It's well-known that macrophages entering the tumor microenvironment lose the ability to aid the immune system in rejecting the tumor, and that they may actually play a role in actively suppressing anti-tumor immunity," said Zanetti. "We believe that transmissible ER stress could be an important initial tumor-derived signal that promotes the 'brainwashing' of macrophages in the tumor microenvironment. It could

be the first event in a cascade that results in the commandeering of macrophages by the tumor."

If so, transmissible ER stress may represent a unifying mechanism that explains at least some of the earliest interactions between tumors and the immune system. "Our paper details the first evidence of this phenomenon," Zanetti said, adding that transmissible ER stress also presents a new, potential target for tumor-specific therapies and drugs.

"Our findings suggest that development of therapies targeted against the tumor ER stress response may be doubly effective," said Zanetti. "Such therapies would target not only the tumor's intrinsic ability to cope with microenvironmental insults, but, at the same time, would impede the tumor cells' ability to nullify the anti-tumor immune response, perhaps allowing our bodies to more easily fight off tumors."

Provided by University of California - San Diego

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