The 'cyberwar' against cancer gets a boost from intelligent nanocarriers

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Two years ago, Prof. Eshel Ben-Jacob of Tel Aviv University's School of Physics and Astronomy and Rice University's Center for Theoretical Biological Physics made the startling discovery that cancer, like an enemy hacker in cyberspace, targets the body's communication network to inflict widespread damage on the entire system. Cancer, he found, possessed special traits for cooperative behavior and used intricate communication to distribute tasks, share resources, and make decisions.

In research published in the Early Edition of the *Proceedings of the National Academy of Sciences*, Prof. Ben-Jacob and researchers from Rice University and the University of Texas M.D. Anderson Cancer Center, the leading cancer treatment center in the U.S., offer new insight

into the lethal interaction between cancer cells and the immune system's communications network. Prof. Ben-Jacob and the study co-authors developed a computer program that models a specific channel of cell-to-cell communication involving exosomes (nanocarriers with crucial cellular "intelligence") that both cancer and immune cells harness to communicate with other cells.

"Recent research has found that cancer is already adept at using a kind of 'cyberwarfare' against the immune system. We studied the interplay between cancer and the immune system to see how we might be able to shift the balance against cancer," said Prof. Ben-Jacob, noting a difference between the innate and the adaptive qualities of the immune system. "In the beginning, cancer is inhibited by the body's innate immunity. But once cancer escapes the immunity, there is a race between the progression of cancer and the ability of the adaptive immune system to recognize and act against it."

Cyberwarfare of the body

"What we are dealing with is cyberwarfare, pure and simple. Cancer uses the immune systems' own communications network to attack not the soldiers but the generals that are coordinating the body's defense," said Prof. Ben-Jacob.

To better understand the role of exosome-mediated cell-to-cell communication in the battle between cancer and the immune system, the researchers created a computer model that captured the exosomal exchange between cancer cells, dendritic cells, and the other cells in the immune system.

The new model is based on earlier research, which showed that dendritic cells, mediators between the body's innate and adaptive immune systems (the former protects against all threats at all times and the latter guards

more efficiently against specific, established dangers), employed exosomes to fulfil their task. The researchers discovered that, overtaken by cancer, these nanocarriers, which contain such vital components as signaling proteins, RNA snippets, and microRNAs, can command cells to change their tasks, placing the entire system at risk.

Finding a better balance between the strong and the weak

According to the new research, three possible cancer states can exist: strong, intermediary, and weak. The intermediary state—in which cancer is neither strong nor weak and in which the immune system is on high alert—could be the key to a new therapeutic approach with reduced side effects. Prof. Ben-Jacob believes it is possible to force cancer from a strong to moderate state, and then from a moderate to weak state, by alternating cycles of radiation or chemotherapy with immune-boosting treatments.

"Our first important discovery is that this situation is due to the exosome-based cyberwar between cancer and the immune system," said Prof. Ben-Jacob. "Without exosomes, the two possible states are only strong-weak and weak-strong. With exosomes, an intermediary state opens a new way to treat cancer using very a different approach."

Prof. Ben-Jacob likened the exchange to a tug-of-war between cancer and the immune system. "The challenge is to be familiar with the battlefield so that we can manipulate cancer therapies to change the balance in favor of the immune system. When cancer is detected, it is almost always in the context of a cancer-immunity competition," said Prof. Ben-Jacob. "We showed that the way to stop and reverse tumor progression without causing strong side effects is an individualized approach of mixed treatments—i.e., four days of radiation followed by a

few days of immune system boosting, followed again by four days of radiation, and so on. If provided in the right order, the treatments could indeed shift the balance toward the immune system's 'victory' in reducing the cancer to the moderate-strong state."

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