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Technion team find proteins that could hold key to cancer growth

• By JUDY SIEGEL

Researchers at the Technion-Israel Institute of Technology's Rappaport Faculty of Medicine have discovered two cancer-suppressing proteins that could hold one key to control cancer cell growth and development. Their "significant discovery" was conducted in the lab of 2004 Nobel Prize co-winner Prof. Aaron Ciechanover and just published in the most-recent edition of the prestigious journal *Cell*.

Ciechanover, who is the president of the Israel Cancer Society, stressed on Sunday that "many more years are required to establish the research and gain a solid understanding of the mechanisms behind the suppression of the tumors. The development of a drug based on this discovery is a possibility, although not a certainty, and the road to such a drug is long and far from simple."

The team was led by research associate Dr. Yelena Kravtsova-Ivantsiv, and included additional research students and colleagues, as well as physicians from the Rambam, Carmel and Hadassah University Medical Centers who are studying tumors and their treatment.

The previously undiscovered proteins were found during ongoing research on the ubiquitin system, an important and vital pathway in the life of the cell responsible for the degradation of defective proteins that could damage the cell if not removed. The ubiquitin system tags these proteins and sends them for destruction in the cellular complex known as the proteasome.

Usually, the proteins that reach the proteasome are completely broken down, but there are some exceptions – and the current line of research examined p105, a long precursor of a key regulator in the cell called NF- κ B. It turns out that p105 can be broken down completely in certain cases following its tagging by ubiquitin, but in other cases it is only cut and shortened and becomes a protein called p50.

NF- κ B has been identified as a link between inflammation and cancer. The hypothesis of the connection between inflammatory processes and cancer was first suggested in 1863 by German pathologist Rudolph Virchow, and it has been confirmed over the years in a long series of studies.

Ever since the discovery nearly three decades ago of NF- κ B, numerous articles have been published linking it to malignant transformation. It is involved in tumors of various organs (prostate, breast, lung, head and neck, large intestine, brain, etc.) in several parallel ways, including inhibition of apoptosis (programmed cell death) normally eliminates transformed cells; acceleration of uncontrolled division of cancer cells; formation of new blood vessels (angiogenesis), which are vital to tumor growth.

As noted, the precursor p105 is "handled" by the ubiquitin system in one of two parallel and equally prevalent ways. It is either destroyed completely or shortened and transformed to p50. The current research deciphers the decision-making mechanism that determines which process will be applied to the protein. When a ubiquitin system component called KPC1 is involved in the process and attaches ubiquitin to p105, the protein is shortened to become p50. When ubiquitination is mediated by another component of the system (and without KPC1), p105 is degraded.

The decision between these two options has significant implications on the cell, as the presence of high levels of KPC1 (which generates p50) and p50 (the product of the process) – with the accompanying disruption of the nor-

mal ratios between the processes – suppresses the malignant growth and apparently protects the healthy tissue. The current research was conducted on models of human tumors grown in mice, as well as on samples of human tumors, and a strong connection was discovered between the suppression of malignancy and the level of the two proteins, clearly indicating that the increased presence of KPC1 and/or p50 in the tissue can protect it from cancerous tumors.