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New understanding of why anti-cancer therapy stops working at a specific stage

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Researchers at the Hebrew University of Jerusalem and in California have achieved a breakthrough in understanding how and why a promising anti-cancer therapy has failed to achieve hoped-for success in killing tumor cells. Their work could lead to new insights into overcoming this impasse.

The problematic therapy investigated involves suppression of the protein mTOR (mammalian target Of Rapamycin). MTOR plays an important role in regulating how cells process molecular signals from their environment, and it is observed as strongly activated in many solid cancers.

Drug-induced suppression of mTOR has until now shown success in causing the death of cancer cells in the outer layers of cancerous tumors, but has been disappointing in clinical trials in dealing with the core of those tumors.

Reduced oxygen supply—hypoxia—is a near-universal feature of solid tumors that can alter how tumors respond to therapies. It was known that the behavior of mTOR signaling is influenced and altered by the condition of hypoxia, but the mechanism to explain this was unknown.

A research team, which included Prof. Emeritus Raphael D. Levine of the Institute of Chemistry at the Hebrew University of Jerusalem and researchers from the California Institute of Technology and the David Geffen School of Medicine at UCLA, investigated whether the influence

of hypoxia on mTOR signaling in model brain cancer systems could explain the poor performance of mTOR drugs. Their work appeared in a recent article in the *Proceedings of the National Academy of Sciences* (*PNAS*) in the US.

For their investigation, they employed a new microchip technology that allowed them to measure the mTOR protein signaling network in individual cancer cells, and they interpreted the results using a new set of theoretical tools derived from the physical sciences. The combined approach permitted the simplification of an otherwise complex biological system.

They found that at a particular level of oxygen starvation (hypoxia) that is common in solid tumors, the mTOR signaling network switches between two sets of properties. At the switching point, the theoretical models predicted that mTOR would be intrinsically unresponsive to drugging.

Furthermore, the combined experiment and theory results indicated that the switch could be interpreted as a type of phase transition, which has not been previously observed in biological systems.

This phase transition is the point of the switch between the two signaling networks and happens very abruptly. The change in signaling means that the body of cells studied no longer responds in the way it did before. In the case of the tumor, the "drugging" of the mTOR ceases, meaning that the tumor is no longer inhibited.

These results have several implications. First, they may explain the poor clinical performance of mTOR inhibitors. Second, they indicate that certain complex biological behaviors, which often confound scientists who are seeking to find effective therapies for human diseases, may be understood by the effective application of experimental and theoretical

tools derived from the physical sciences.

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