Tumor treatment: the fight against a System

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ABSTRACT

The treatment of cancer is likely to benefit from studies on system properties that can be understood at the molecular as well as the cellular level. During its microevolution, a tumor may have developed system properties, such as autonomous growth, angiogenesis, resistance against attacks from the immune system, or genetic instability. As an "organ" it shows a certain robustness and is able to defend itself against attacks. Thereby it will maintain homeostasis. Interfering with one of these properties may destroy the system. More knowledge on the system will help finding the Achilles' heel, the weakest spot, causing a minimal toxicity to the patient.

In a macroscopic tumor the cancer cells support the formation of new endothelial cells to replace the dead cells, by the excretion of angiogenic factors, such as VEGF and bFGF. The concentration of these factors must be high enough for endothelial cell proliferation. The mutual dependence of cancer and endothelial cells means that attack of either cell type can lead to corruption of the system. Below a critical point of cancer cell density and endothelial cell density the cancer will not be able to keep its concentration of angiogenic factors at a high enough level. This leads to destruction of blood capillaries, followed by cancer cell death, leading to even lower concentrations of angiogenic factors, etc. In line with this, recently a dramatic difference by a factor 17 was reported for microvessel density between macroscopic and microscopic breast tumors [1]. It has been proposed that a shift in the balance between pro and anti-angiogenic factors forms a "switch" that turns the dormant state into a macroscopic tumor with its own angiogenesis [2,3].

In addition, here a "toggle switch" is proposed. This critical "toggle point" is intriguing and calls for further investigation from a Systems perspective. Further reduction beyond this point will follow "by itself"' towards a microscopic dormant tumor, allowing nutrient supply by diffusion from the environment. When this critical point has not been passed and the treatment stops temporarily, the system restores itself to larger dimensions. This could explain a superior effect of the same daily dose of endostatin given per continuous infusion when compared to i.p. doses [4]. Another implication of this model is that in combinations of chemotherapy and anti-angiogenesis drugs, it is better to administer sequentially rather than simultaneously, as reduction in endothelial cell density will lead to reduction of cancer density anyhow, and vice versa.

To our knowledge, such a simple model of a toggle switch only based on both cancer cell density and endothelial cell density, has not yet been published. The quality of the toggle switch (the irreversibility of the system) with respect to the natural variations in time around this critical point deserves further investigation.

REFERENCES

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