



Opinion

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# Stress, Glucocorticoid and Cancer: Happy Tumor Cells



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## Opinion

The cells derived from a primary tumor that migrate and grow into other organs form the metastases, responsible for most cancer-related deaths, which may arise soon after diagnosis or many years after the initial treatment [1]. This latency period, from primary tumor to recurrence or distant metastasis, in which the tumor does not induce any clinical symptoms, but has the potential to reactivate, is called tumor dormancy. In this phase the residual tumor cells remain in a state of proliferative inertia, while retaining the ability to replicate. Sleeping neoplastic cells, which are present in patients recovered from a tumor or even in healthy individuals, remain vital but do not multiply, until an event, not always identified and identifiable, reactivates the proliferative genetic program, temporarily blocked [2].

Despite recent advances in the field of oncology, the molecular mechanisms underlying dormancy and awakening of the neoplastic cell are not well known. Cancer dormant cells receive and send signals to the tumor microenvironment and this bidirectional dialogue - in which the microenvironment modifies the tumor cell and vice versa - is critical for the fate of the neoplastic cell. To simplify, favorable interactions between the neoplastic cell and its microenvironment - consisting of various cell types, including the cells of the immune system - will make cancer cell dormant, non-proliferating and happy, while unfavorable interactions will contribute to the replication of the neoplastic cell and to the induction of a relapse [3]. A crucial role for the happiness of neoplastic cells is played by the immune system, with the function of active immune-surveillance. The immune cells of the tumor microenvironment regulate, in fact, the balance between the processes of proliferation, differentiation and death and can, if functionally active, induce the expression of genes that suppress the metastases and favor the dormancy [4]. However, the occurrence of stressful signals - through the involvement of the immune system, which modifies the interactions of the tumor cell with its microenvironment - can shift the balance towards the reactivation of proliferative programs [4].

Psychological conditions affect the development and/or progression of cancer; especially if the diagnosis of cancer has already been made. In fact, cancer patients often live in a state of

anxiety and depression due to therapeutic treatment or progression of the disease. The psychoneuroendocrinology (PNEI) is the science that explains how the patient's psychological condition can influence the cells of his immune system and therefore tumor growth [5]. Unfortunately, despite some stress signs are measurable in the immune system of many patients with cancer, these are not yet universally accepted by the scientific community and, therefore, are not considered diagnostic and prognostic markers.

Any stress condition increases endogenous glucocorticoids (GCs), catecholamines and other neurotransmitters (stress factors) that can activate, -with different mechanisms, but, above all, with an action at the level of the immune system -the cell proliferative program of dormant cancer cells, in proliferative rest [6]. Therefore, stress -physical or psychological -by changing the relationship between the sleeping tumor cell and the microenvironment, can change the fate of a tumor.

One of the main effectors of the stress response is the hypothalamic-pituitary-adrenal axis, which responds to stress increasing blood GCs, which, acting on the target organs and on the metabolism, constitute an important part of the body adaptive response to the stress [7]. However, when stress becomes chronic and/or in the organism there are dormant neoplastic cells, the adaptive, functionally useful response, becomes harmful. In fact, GCs, with different mechanisms, promote the development of the tumor [7]. In particular, they contribute to the inhibition of systemic and tumor microenvironment immune cells [8] and, with molecular mechanisms not yet fully known, reawaken the happy cancer cells, i.e. reactivate the proliferative program of dormant tumor cells inducing tumor growth, progression and metastasis [9]. Of note, GCs are the most commonly used anti-inflammatory and immunomodulatory agents [10].

One of the mechanisms by which the GCs reactivate the dormant cells of melanoma, involves a protein called Glucocorticoid-Induced Leucine Zipper (GILZ) [11].

It is known that most GC-elicited effects result from the transcriptional regulation of GC receptor target genes [12]. Among

these genes, GCs increase the transcription of GILZ that mediates many anti-inflammatory and immunosuppressive effects of GCs [13]. Recently, it has been demonstrated that GILZ signaling, by activation of molecules regulating the cell cycle, such as FOXO3A and its downstream target p21CIP1, awakens dormant melanoma cells, induces cell proliferation and tumor growth. Consequently, GILZ's suppression causes cellular dormancy, contributing to melanoma inactivity [14]. Although the role of GILZ has been studied only in the melanoma dormant cells, if GILZ would play a general regulatory function in tumor dormancy, this could open the way to future investigation on signals and/or drugs able to modulate GILZ expression in sleeper cancer cells.

In conclusion, endogenous GCs, acting on several target cells, regulate the physiological processes of proliferation, death and cell differentiation. When GCs are administered as anti-inflammatory drugs, in patients with cancer the final outcome is the sum of their effects on cells, receptors, adhesion molecules and cytokines and this explains why most of the time GCs favor neoplastic growth, but sometimes they can also inhibit it [15,16]. However, for the dormant cancer cells, the absence of stress - and hence low GC levels (but also low levels of other stress hormones) -can constitute, using a deliberately exaggerated term, the happiness.

There is a kind of direct causality between the relations of the individual with his environment and those of the tumor cell with its microenvironment. The positive interactions of the individual with his environment, in fact, induce positive interactions of the neoplastic cell with its microenvironment. On the contrary, the stress of the individual generates an imbalance between the neoplastic cell and microenvironment immune system, with consequent mitotic reawakening of the dormant tumor cell [6].

The cell happiness of and our happiness concur, therefore, to protect us from cancer? This concept of ancient wisdom seems to gain new strength and more consolidated scientific bases.

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