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**Cancer as a Dysregulated Regenerative
Response: A Functional Hypothesis on
Systemic Signaling Collapse**

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Cancer as a Dysregulated Regenerative Response: A Functional Hypothesis on Systemic Signaling Collapse

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Abstract

This article introduces a new hypothesis regarding the systemic origin of cancer, framing it not as a random accumulation of malignant mutations but as a dysregulated continuation of an initially adaptive regenerative process. It proposes that chronic or unresolved tissue distress, whether inflammatory, metabolic, or biochemical, activates a repair program mediated by cytokines, immune signals, and growth factors. When internal feedback mechanisms, such as neuroendocrine, immune, or cellular signaling systems, fail to indicate completion, this regenerative response persists abnormally. The result is the emergence of a proliferative state that escapes systemic modulation. This model suggests that tumors are not pathological anomalies, but maladaptive extensions of biological repair efforts that have lost regulatory coherence. It opens a novel conceptual path for interpreting oncogenesis as a process of systemic miscommunication and calls for therapeutic strategies focused on signal recalibration and physiological reintegration, rather than exclusive cytotoxic eradication.

Keywords

Cancer; Regeneration; Homeostasis; Cellular signaling; Leukemia; Systemic feedback; Biological communication

Introduction

Current oncological paradigms describe cancer as the result of uncontrolled cellular proliferation triggered by genetic mutations and external aggressors. The prevailing therapeutic framework has been predominantly cytotoxic, aiming to eliminate the tumor through chemotherapy, radiotherapy, or surgical excision (Hanahan and Weinberg 2011). However, this reductionist approach often fails to account for why certain malignancies arise in individuals without evident genetic predispositions or environmental risk factors,

and why some treatments result in systemic collapse rather than resolution (Greaves 2018). These clinical inconsistencies raise a fundamental question: what if cancer is not merely a pathological error, but an initially adaptive biological response that fails to self-terminate due to dysregulation in internal signaling pathways?

The Hypothesis

Cancer may be initiated by a localized or systemic signal of distress, a tissue that is damaged, inflamed, metabolically overloaded, or biochemically imbalanced (Balkwill and Mantovani 2001, Medzhitov 2008, Warburg 1956). In such contexts, the body activates a regenerative cascade involving cytokines, growth factors, immune cell recruitment, and localized proliferation (Medzhitov 2008). However, when internal feedback mechanisms fail to recognize that tissue repair is complete, due to chronic inflammation, neuroendocrine dysregulation, or immune overload, the regenerative process becomes persistent and dysregulated. The result is a tumor: not a product of cellular chaos, but the extension of a biological program that has lost its regulatory resolution.

Supporting Evidence and Functional Examples

Multiple cancers arise in tissues that exhibit prior signs of chronic dysfunction. Hepatocellular carcinomas, for instance, often develop in livers with persistent inflammation or cirrhosis (Balkwill and Mantovani 2001). Cervical cancers are frequently associated with sustained HPV infections and hormonal dysregulation. Pancreatic cancer is commonly linked to insulin resistance and metabolic exhaustion, forming an environment of unresolved biochemical stress (Medzhitov 2008). In these cases, the tissue microenvironment reflects a regenerative attempt to restore homeostasis, but this response may become excessive or poorly modulated. Leukemia, the central example in this hypothesis, represents a systemic collapse of hematopoietic regulation. Clinical manifestations such as fatigue, immunodeficiency, bone pain, pallor, anorexia, and hemorrhage are not random consequences, but functional outcomes of a medullary signaling system that has lost its integrative capacity.

Model Overview

Phase 1 – Silent or chronic suffering in a specific tissue or system, such as unresolved inflammation or metabolic overload (Medzhitov 2008).

Phase 2 – Activation of regenerative cellular responses, involving cytokines, growth factors, and local proliferation (Hanahan and Weinberg 2011, Medzhitov 2008).

Phase 3 – Failure in the feedback signaling that should terminate the repair process.

Phase 4 – Persistent, disoriented cellular multiplication in the absence of regulatory checkpoints.

Phase 5 – Immune counterattack or systemic collapse resulting from prolonged overstimulation or immune exhaustion.

Phase 6 – Generalized spread (metastasis) or total breakdown of functional control, as seen in hematological malignancies like leukemia.

Conclusions

This hypothesis reinterprets cancer not as a random pathological accident, but as the consequence of a prolonged regenerative signal that has lost its modulatory control. By framing cancer as a systemic communication failure, this model suggests that tumors may arise from biologically coherent but dysregulated responses to unresolved cellular suffering. Rather than simply categorizing tumors as malignant errors, this view opens a new theoretical path: restoring physiological balance through recalibration of endogenous signaling systems. While conceptually disruptive, this proposal is anchored in established physiological principles (Hanahan and Weinberg 2011, Medzhitov 2008) and invites further investigation into therapeutic strategies aimed not solely at destruction, but at reintegration of systemic control.

Conflicts of interest

The authors have declared that no competing interests exist.

References

- Balkwill F, Mantovani A (2001) Inflammation and cancer: back to Virchow? *The Lancet* 357 (9255): 539-545. [https://doi.org/10.1016/S0140-6736\(00\)04046-0](https://doi.org/10.1016/S0140-6736(00)04046-0)
- Greaves M (2018) A causal mechanism for childhood acute lymphoblastic leukemia. *Nature Reviews Cancer* 18 (8): 471-484. <https://doi.org/10.1038/s41568-018-0015-6>
- Hanahan D, Weinberg RA (2011) Hallmarks of cancer: the next generation. *Cell* 144 (5): 646-674. <https://doi.org/10.1016/j.cell.2011.02.013>
- Medzhitov R (2008) Origin and physiological roles of inflammation. *Nature* 454 (7203): 428-435. <https://doi.org/10.1038/nature07201>
- Warburg O (1956) On the origin of cancer cells. *Science* 123 (3191): 309-314. <https://doi.org/10.1126/science.123.3191.309>