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Archives of Clinical Investigation

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Review Article

Regression of Oncological Formations at the Tissue Level and Intercellular Fluid

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Received date: September 05, 2024; Accepted date: September 1, 2024; Published date: September 29, 2024

Citation: Evgeniy B. Din, (2025), Regression of Oncological Formations at the Tissue Level and Intercellular Fluid, *Archives of Clinical Investigation*, 4(5); **DOI:**10.31579/2834-8087/044

Abstract

Therapy of the interstitial fluid before the destruction of intercellular connections has two interrelated directions, firstly, a decrease in the interstitial fluid (interstitial fluid) and normalization of the tumor microclimate before the intercellular connections are destroyed, and secondly, the destruction of intercellular connections as part of therapy (to increase drug penetration. The interstitial fluid and the surrounding ECM environment come to the fore, and the intercellular connections themselves play a modifying role. The interstitial fluid (interstitial fluid) fills the space around the cells in the tumor. Often, its pressure is higher than normal (IFP), which limits the penetration of drugs and immune cells, contributes to hypoxia and the formation of an oxidative environment. Reducing IFP and loosening ECM improve the delivery of immunotherapy and weaken the intercellular connections of the tumor. Immune therapy focused on the interstitial fluid and ECM is aimed at destroying the connections of tumor cells, improving the penetration of immune cells into the tumor by reducing IFP and loosening ECM. Modification of intercellular connections and ECM occurs at first stages of treatment and reduces aggressive tumor growth. Modern therapies are focused on controlled modification of bonds with cytotoxic or immunotherapeutic agents. The regression effect depends on the tumor type, its microenvironment, stage, and combination of drugs used.

Keywords: therapy; intercellular fluid; cancer tumor; regression of intercellular connections

Introduction

Oncology is a potentially reversible, nonlinear complex system with continuous spatial information organization of tissues. Data on tissue morphogenesis confirm this paradigm [1]. Oncology, as a pathological phenomenon, occurs at the tissue level, not the cellular level. Spontaneous regression of cancerous tumors also indicates that this is a pathological phenomenon that occurs at the tissue level, not the cellular level [2-4].

Research is underway on the regression of cancerous tumors by changing the structure and quality of the intercellular fluid to the disruption of the intercellular connections of cancer cells. We are talking about extracellular intercellular fluid in malignant tissues and about therapy [5]. This is the fluid in the intercellular space of the tumor, surrounding cancer cells and stromal elements.

Modern techniques: IMRT, VMAT, SBRT (stereotactic radiosurgery), proton therapy lead to a rapid reduction in tumor volume and are used as the main treatment or in combination with systemic therapy.

Radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, high-dynamic focused ultrasound (HIFU) are used locally for small tumors in the liver, lungs, kidneys, bones and other locations.

Radionuclide therapy with radionuclides: Lutetium-177-PSMA for some forms of prostate cancer; Radium-223 for bone-resistant regression in metastatic prostate cancer; new alpha or beta emitting agents in development.

Experimental approaches based on CRISPR/Cas9 and other systems for correcting mutations, turning off oncogenes or delivering therapeutic genes. In the clinic, so far mainly as part of trials.

Nanocomplexes for diagnostic and therapeutic theragnostic. The use of combined tumor screening and treatment through one module: diagnose and treat at the same time (theragnostic) is being actively studied.

Radiomics and artificial intelligence for predicting treatment response and regression based on images and clinical and genetic data; optimization of planning of local and systemic approaches, monitoring tumor dynamics in real time are at the stage of clinical trials.

Combination therapy aimed at multiple oncogenic mutations is based on SMT method [6].

International Translational Medicine quickly introduces modern oncological technologies in World Healthcare [7].

2. The role of intercellular fluid of adenocarcinoma in its intercellular connections

The intercellular fluid in an adenocarcinoma tumor forms a microenvironment that affects the strength and functionality of intercellular junctions. The components of this fluid (imines: Ca2+, pH, growth factors, cytokines, enzymes, salts) and the accompanying tissue microstructure (ECM, fibroblasts-CAF, vascular permeability) determine how well cells adhere to each other and how they communicate through intercellular contacts. Let us consider the main aspects of the role of the intercellular fluid in intercellular junctions of adenocarcinoma:

1. Ca2+ and calcium-dependent contacts:

-Adhesin junctions and desmosomes depend on the level of Ca2+ in the external environment. Changes in the concentration of Ca2+ in the intercellular fluid can weaken cell adhesion, reduce the stability of E-cadherin and other cadherins, which contribute to the disintegration of intercellular junctions and EMT (epithelial-mesenchymal transformation).

2. Gap junctions:

- Communication between cells via connexons regulates the transfer of small-component molecules. In tumors, functional gaps are often reduced, which changes cell coordination and contributes to tissue disorganization.

3. Desmosomes and their role:

- Desmosomes depend on calcium and the corresponding cadherins. Damage to the intercellular fluid, reduced Ca2+ concentration or activation of proteases in the microenvironment contribute to the disintegration of desmosomes and weakening of the strength of the cellular network.

4. Effect of ECM and mechanical signals:

- The intercellular fluid is not isolated from the ECM. The microfluidic environment, interacting with the ECM (collagen, fibronectin, etc.), transmits mechanical signals through integrins to the cytoskeleton. This changes the polarity of cells and the stability of intercellular connections.

5. Role of acidity, metabolism and MMPs:

- Tumors often have an acidotic environment (low pH) and high lactate levels. This activates metalloproteinases (MMPs), which degrade the ECM and junctional components, reducing the strength of intercellular contacts.

Summary:

Adenocarcinoma intercellular fluid plays a key role in maintaining or destroying intercellular connections via Ca2+, pH, signaling molecules and the activity of ECM remodeling enzymes.

Therapeutic changes in the composition and biochemical state of the intercellular fluid contribute to the weakening of intercellular connections and adenocarcinoma regression.

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3. Regression of cancer cell connections by therapy of intercellular fluid

Research is being conducted on the regression of cancerous formations by changing the structure and quality of the intercellular fluid until the intercellular connections of cancer cells are disrupted. Consider three key aspects of therapy-induced regression:

1) Disruption or weakening of cell-cell and cell-ECM contacts;

2) Redistribution and remodeling of ECM and decreased tumor support;

3) Changes in the composition and physicochemical properties of the interstitial fluid.

1. Regression of cell-cell connections and changes in TIF.

1.1 Disruption/modulation of cell contacts:

In response to treatment, cells can switch from a tightly connected state to a more separated configuration (often through regulation of E-cadherin, EMT/MET pathways, Want/TGF-β signaling pathways).

This is accompanied by a decrease in the transparency of cell-cell contacts and changes in tissue plasticity.

1.2. ECM remodeling:

Decreased collagen I/III density, degeneration of some ECM components or their redistribution.

Decreased tissue stiffness and intercellular pressure fluctuations, which affects drug diffusion and cell-cell signaling.

1.3. Effect on interstitial fluid and perfusion:

Antiangiogenic therapy and “normalization” of vessels can reduce excessive vascular permeability, decrease interstitial pressure and improve tissue ventilation.

Reduction of hypoxia and improvement of interstitial fluid drainage reduce local foci of regression and promote more effective penetration of therapeutic agents.

ECM-targeted therapy (e.g., hyaluronic acid reduction or reduction of collagen and fibrosis) reduces intercellular resistance to drug transport.

1.4. Effect on the immune component of TIF:

Changes in the cytokine landscape and infiltration of immune system cells (T-lymphocytes, macrophages) change the composition and quality of TIF, which can promote or inhibit tumor regression.

1.5. Specific therapeutic approaches and their impact:

Vascular normalization (anti-angiogenic therapy): reduces interval leakage and interstitial fluid pressure (IFP), improves drug convection.

ECM-targeted therapy (e.g., hyaluronic acid degradation, antifibrotic agents): loosens the dense scar network, facilitates tumor penetration.

-Inhibitors of signaling pathways affecting cell-cell contacts (e.g., EMT pathways): can promote contact remodeling and change resistance to therapy.

Combinations of radiotherapy/chemotherapy with immunotherapy: affect TIF through changes in vascular permeability and cytokine profile.

2. Practical examples and clinical implications:

Involvement of hyaluronidase and analogs (hyaluronic acid degradation) with chemotherapy in some tumors reduces intercellular pressure, improves drug penetration, and may facilitate regression of tumor components.

Normalization of the vasculature when combining antiangiogenic therapy with chemotherapy may increase drug delivery to the tumor and accelerate regression of cell-cell junctions by improving the microenvironment.

ECM modulators (e.g., blocking TGF-β signaling or using antifibrotic agents) may reduce tissue stress and decrease the strength of cell-ECM

junctions, which affects regression and spread of therapy throughout the tissue.

Immunotherapy may redistribute TIF composition, enhancing or weakening the infiltration of certain immune-active cells, which indirectly affects regression of cell-cell junctions due to changes in the microenvironment.

3. Methods for assessing changes:

Histological and immunohistochemical markers: E-cadherin, Claudins, connexins; EMT/MET markers; collagen/ECM components. - Measurement of intercellular pressure and perfusion: direct and indirect methods (multifunctional kinetic tests, DCE-MRI, ultrasound elastography).

TIF analyses: composition of cytokines, growth factors, metabolites; microdissection/mass spectrometry.

-Regression assessment: tumor regression grades, changes in cell density and fibrous tissue, dynamics of vessel volume and structure.

4. Tissue-level cancer regression

Tissue-level cancer regression is a change in tumor tissue, either spontaneously or under the influence of treatment, in which the number of viable cancer cells decreases and the tissue is replaced by fibrous/remodeled tissue. These changes are assessed at the level of tissue samples taken using histology.

Key mechanisms at the tissue level:

Clinical therapeutic cell death: apoptosis, programmed cell death; focal necrosis; mitochondrial and DNA disorganization.

Decreased proliferation: decreased Ki-67 and other cell cycle markers; cell cycle inhibition.

Immune regulation: infiltration of cytotoxic T lymphocytes, macrophages; cytokine microclimate that supports the fight against the tumor.

Vascular regression and impaired tumor nutrition: decreased microvascular density, vascular bed reservation; hypoxia leading to cell death.

Tissue remodeling: fibrous replacement tissue, desmoplasia around regression zones; scar formation.

Differentiation/senescence of tumor cells under the influence of therapy.

Interaction with stroma: activated tumor fibroblasts, altered microenvironment, etc.

Histopathological signs of regression:

Presence of necrosis and/or apoptotic bodies in tumor foci.

Decreased number of viable tumor cells; sparse tissue or scar tissue “skeleton”.

Fibrous/desmoplastic tissue at the tumor site (scar tissue).

Immune cell infiltrates around residual tumor.

-Decreased proliferative activity (fewer mitoses).

Residual viable tumor cells may be fragmentary; sometimes only a fragment of stroma or cysts/lesions remain at the site of regression.

In some cases, calcification or cystic transformation may be seen.

How tissue regression is assessed:

Different tumor regression scales after neoadjuvant therapy (TRG): for example, Mansard, Evans, other local schemes. General ideas:

Complete regression — absence of viable tumor in samples.

Partial regression — variable proportion of viable tissue and degree of fibrous remodeling.

Pathological studies: pathological complete regression (pace) in some tumor zones (colorectal cancer after preoperative therapy, etc.).

Practical aspects:

- It is important to take into account tumor heterogeneity: regression can be uneven, residual foci of life can be localized in certain areas.

- Assessment is carried out based on postoperative/biopsy materials, sometimes with several samples from different zones.

Typical examples by cancer type:

Colorectal cancer after neoadjuvant chemotherapy/radiotherapy: TRG scales are applicable, assess residual tumor area and fibrosis.

Gastric/esophageal cancer: regression according to Mansard or similar scales, reveals a combination of fibrosis and reduced tumor cells.

5. Regression of prostate adenocarcinoma tissue cancer cells by hormonal therapy

Regression of prostate adenocarcinoma cancer cells under hormonal therapy is achieved through suppression of the androgen receptor signal and a decrease in testosterone. This is most often clinically manifested as a decrease in PSA and a decrease in tumor load against the background of a cytostatic effect (cycle arrest, apoptosis).

Regression assessment:

Reduction in tumor volume and/or number of active cells (clinical and imaging). Reduction in AR signaling: decreased expression of AR targets (PSA, PROT, cell cycles) and slower proliferation.

Biochemical regression: decreased PSA levels, sometimes correlating with clinical response.

Microenvironment and parallel pathways: decreased local androgen synthesis and interaction with other signaling pathways (IGF1R, HER2, etc.).

Main hormonal therapy regimens:

GnRH agonists/antagonists (LHRH analogues, such as leuprolide, triptolide) and/or antagonists (deguelin): reduce testosterone to castration levels. The effect is inhibition of the AR signal and growth retardation.

First-generation antiandrogens (bicalutamide, flutamide) — competitive block of AR gives a regression effect.

Second-generation AR inhibitors (enzalutamide, apalutamide): more powerful blockade of AR transport to the nucleus, decreased expression of AR targets lead to more durable regression and delayed progression compared to first-generation drugs. CYP17A1 inhibitors (abiraterone): reduce intra-tissue synthesis of androgens, effective both in hormone-sensitive status and in CRPC in combination with prednisone.

Combination hormonal therapy: ADT + AR-planned or + CYP17A1 inhibitors can give a more pronounced rgrissino effect in HSPC (hormone-sensitive local and metastatic disease).

Regression on the cellular level:

AR blockade reduces receptor translocation into the nucleus and transcription of AR targets; cells slow down division (G1 arrest) and undergo apoptosis.

Decreased expression of proliferative genes, decreased mitotic index. Decreased intra-tissue androgen levels and effects on the paracrine/mepacrine environment of the tumor.

Resistance mechanisms and CRPC concepts:

AR mutations (e.g., F876L, T878A) and the AR splice variant AR-V7, which change sensitivity to AR inhibitors.

Enhancement of alternative growth pathways (PI3K/AKT/mTOR, MAPK).

Intracellular androgen synthesis within the tumor, neuroendocrine differentiation. - The importance of the microenvironment and epithelial-membrane dynamics.

Regression parameters:

Biochemical: PSA decline, often ≥50% in the first 4-12 weeks correlates with better outcomes. - Clinical-radiological: RECIST imaging is less applicable for bone metastases; for bone lesions, PCWG3 criteria and assessment of changes on CT/MRI, PET (PSMA-PET) is used whenever possible.

Micro markers: Ki-67, AR up-regulation/down-regulation, AR-V7 status, among others, indicate the risk of resistance to AR inhibitors.

In the clinic, PSA response, imaging dynamics, and patient symptoms are often taken into account.

Typical clinical scenarios:

Metastatic hormone-sensitive prostate cancer (mHSPC): initiation of ADT (or deguelin) results in significant regression.

CRPC: continued hormonal suppression in combination with AR inhibitors or abiraterone gives temporary regression or stabilization, new strategies include PSMA targeting, radio modification and combinations with immune therapy.

LHRH agonists (Gosselin, berlin, etc.) with PSA control give significant regression.

6. Conclusion

Genome sequencing of cancer and normal tissues, along with single-cell transcriptomics, continues to yield results that challenge the idea that cancer is a genetic disease. The dynamics of cell states and tissue fields arise from the collective action of genes and cells in their morphogenetic context.

Some researchers view cancer as a problem of cellular differentiation. In reality, a tumor contains thousands of genetically distinct, independent cell lineages, resulting in intratumorally genetic heterogeneity that is a shock to the world of precision oncology [8,9]. Normalization of a cancer cell is achieved through physical contact with an appropriate embryonic field. Phenotypic transitions are controlled by a complex tissue context, which implies the participation of multiple, often poorly understood, coordinated signals. There is no simple correspondence (i.e., 1:1 correspondence) between genotype and phenotype. Genes directly encode proteins, not phenotypes, and do not act alone. Gene loci interact with each other via the regulatory proteins they encode, which together form the cellular phenotype [10-11]. This brings us to the tissue-level processes.

Cancer as a tissue-based disease according to the field theory of tissue organization of carcinogenesis. All cells of the body are exposed to the carcinogen. From the perspective of developmental biology, the question is: what is the target of the carcinogen: the epithelium, the stroma, or both? This question should be answered with a practical tool for conducting research [12-27]. ChromoGen technology can investigate how DNA mutations alter chromatin structure, linking this to disease [28].

References

1. Michelin R, Grushecky WJM. (2023) Reimagining Cancer: Moving from the Cellular to the Tissue Level. Cancer Res.; 83:173–180
2. Evgeny Bryn din. Neutralization of carcinomas by balanced mechanisms of body systems. . Clinical Research and Studies, 4(3);
3. Evgeny Bryn din (2025.). Aspects of Spontaneous Regression of Oncological Necrotic Tissue. Cancer Research and Cellular Therapeutics, 9(5).
4. Evgeny Bryn din. (2025). Elimination of Cancerous Tumors of Different Organs by Intelligent Cell Therapy and Spontaneous Regression. Cancer Research and Cellular Therapeutics, 9(5);
5. Wagner M and Wiig H (2015) Tumor interstitial fluid formation, characterization, and clinical
6. implications. Front. Oncol. 5:115.
7. Levine AJ, Jenkins NA, (2019) Copeland NG. The roles of initiating truncal mutations in human cancers: the order of mutations and tumor cell type matters. Cancer Cell.;35(1):10–15.
8. Evgeny Bryn din (2025). International Translational Medicine in World Healthcare. Weblog Journal of Clinical Case Reports.
9. Huang S. (2012) The molecular and mathematical basis of Waddington's epigenetic landscape: a framework for post-Darwinian biology? Bioassays;34(2):149–157. pmid:22102361
10. Gerlinger M, Horsnell S, Larkin J, Rowan AJ, Salm MP, Varela I, (2014) et al. Genomic architecture and evolution of clear cell renal cell carcinomas defined by multiregional sequencing. Nat Genet.;46(3):225–233.
11. Ling S, Hu Z, Yang Z, Yang F, Li Y, Lin P, (2015) et al. Extremely high genetic diversity in a single tumor point to prevalence of non-Darwinian cell evolution. Proc Natl Accad Sci U S A.;112(47): E6496-505.
12. Shakina Y, Bloechl B, Moran K, Maslova A, Munro A, Carragher N, et al. Cytoplasmic link RNAs nucleate signaling pathways to define metastable state dynamics and determine phenotypic output. 2024.
13. Liu J. (2020;)The "life code": a theory that unifies the human life cycle and the origin of human tumors. Semin Cancer Biol. 60:380–397.
14. Sonnenschein C, (2020) Soto AM. Over a century of cancer research: inconvenient truths and promising leads. Plows Biol.;18(4): e3000670
15. Marine J-C, Dawson S-J, Dawson MA. Non-genetic mechanisms of therapeutic resistance in cancer. Nat Rev Cancer. 2020;20(12):743–756.
16. Bell CC, Galan O (2020;). Principles and mechanisms of non-genetic resistance in cancer. Br J Cancer. 122(4):465–472.
17. Soto AM, Sonnenschein C. (2021) The cancer puzzle: welcome to organicism. Prog Biopsy's Mol Biol.; 165:114–119.
18. Gutierrez C, Al 'Khafaji AM, Brenner E, Johnson KE, Gohil SH, Lin Z, (2021;) et al. Multifunctional barcoding with Clon Mapper enables high-resolution study of clonal dynamics during tumor evolution and treatment. Nat Cancer. 2(7):758–772.
19. Huang S. (2021) Reconciling non-genetic plasticity with somatic evolution in cancer. Trends Cancer.;7(4):309–322.
20. Bissell MJ, (2021) editors. Rethinking cancer: a new paradigm for the post-genomics era Vienna series in theoretical biology. Cambridge, MA: MIT Press; p. 456.
21. Hanahan D. Hallmarks of cancer: new dimensions. Cancer Disco. 2022;12(1):31–46. pmid:35022204

22. Monti N, Verna R (2022,) Primarolo A, Quique A, Bizzarri M, Fedeli V. Paradoxical behavior of oncogenes undermines the somatic mutation theory. Biomolecules.;12(5):662.
23. Liu J, Niu N, Li X, Zhang X, Sood AK. 2022;) The life cycle of polyploid giant cancer cells and dormancy in cancer: opportunities for novel therapeutic interventions. Semin Cancer Biol. 81:132–144.
24. Sharma V, Letson J, Furuta S. Fibrous stroma: driver and passenger in cancer development. Sci Signal. 2022;15(724): eabg3449. pmid:35258999
25. Sáez M, Briscoe J, Rand DA (2022). Dynamical landscapes of cell fate decisions. Interface Focus.;12(4):20220002.
26. Gravenor FV, Shchurov DG, Malinovsky VV (2023). Multiple linear regression analysis of cancer treatment effectiveness at the level of constituent entities in the Russian Federation. Medical Technologies. Assessment and Choice.;45(1):9 26.
27. Strauss B, Bertolo M, Ernberg I, Demarchelier R, Grushecky WJM. (2023) Reimagining cancer: moving from the cellular to the tissue level. Cancer Res.;83(2):173–180.
28. Gujral C, Turova D, Ima cave M, Luquette LJ, Miry LA. Is tumor mutational burden predictive of response to immunotherapy? life Sciences Publications; 2024.
29. Sui Huang, Ana M. Soto, (2025.) Carlos Sonnenschein. The end of the genetic paradigm of cancer.
30. Greg Schuette, Zhoushan Lao, Bin Zhang. Chromogen. (2025): Diffusion model predicts single-cell chromatin conformations. Science Advances, Volume 11. Is.5. pp. 1-10