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Modeling Tumor Initiation as Ricci Flow

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Abstract

Small variations in magnetic fields can be environmental stresses. For example cell phones, which give off very weak magnetic fields. It is a question, whether these magnetic fields cause brain tumors in cell-phone users. We can model cancer as invasion from social, through psychological to deepest molecular level by Ricci flow. Mechanism of integrated stress response starts with rapid hormone induced changes in receptor conformation which lead to slower modulations of gene transcription. Inhibition of programmed cell death is a major aspect of tumorigenesis (by oncogenic transcription factors NF-κB, STAT3) through upregulation of survival genes. The afferent input from the limbic network conveys purely psychological stress reactions to the HPA axis. Even dominant oncogenes such as v-Src or K-Ras are unable to induce cancer in adult animals without injury. A strong tumor-associated inflammatory response is initiated by the dynamics of Ricci flow collapsing into an injury point that becomes a rounder cellular dysfunction. Tufts biologists show bioelectrical signals control tumors arising from cancer-causing genes; fatty acid involved in process. The have proved, that cancer, bioelectrical signals and the microbiome are connected.

Keywords: Tumor initiation; Invasion; Ricci flow; Bioelectric control; Receptor conformation; Gene transcription; Programmed cell death; NF-κB; STAT3; HPA-axis; Oncogenes; Tissue injury

Bioelectrical Signals from Distant Cells Control the Incidence of Tumors

In a series of recent studies it is evident that social conflicts including interpersonal difficulties can also have detrimental influences on health. Chronic conflictual interactions foster low-grade systemic inflammation contributes to evolution of psychiatric, infectious, metabolic diseases and cancer [1]. Those who expressed greater hostility showed in the laboratory higher levels of the inflammatory cytokines interleukin (IL-6) and tumor necrosis factor α (TNF-α).Quality of interpersonal relations relates to two major biomarkers of systemic inflammation: C-reactive protein (CRP) and interleukin IL-6. In the molecular signaling pathways is important the expression of messenger ribonucleic acid (mRNA) for the chief proinflammatory transcription factor, nuclear factor κB (NFκB) and the glucocorticoid receptor (GR). GR is mediating induction of inhibitor of κB (NFκB), a molecule that sequesters NFκB in the cytosol and prevents it from switching on proinflammatory genes. Social difficulties provoke cortisol abnormalities, which over time foster resistance to glucocorticoids and expression of inflammatory mediators. Corticosteroids coordinate the expression of genes in cell metabolism and synaptic transmission. Signaling in limbic neurons can be regulated also through interaction of GR with transcription factors, such as nuclear factor κB (NFκB) and activator protein 1 (AP1). Stress-related changes leading to expression of the inflammatory cytokines can have profound influences on social behavior [2].

Recently, the developmental biologists at Tufts University, using a tadpole model, have shown that bioelectrical signals from distant cells control the incidence of tumors arising from cancer-causing genes and that this process is impacted by levels of a common fatty acid produced by bacteria found in the tadpole and also in humans.

Metastasis Needs Close Collaboration between Cancer Elements

Recent studies show that metastasis needs close collaboration between cancer cells, immune, inflammatory cells, and stromal elements. It can be differentiated four major part of metastasis: First part consists from epithelial-mesenchymal transition, cancer cells get fibroblastoid characteristics which increase their motility and allow them to invade epithelial linings/basal membranes and reach efferent blood vessels or lymphatics. Loss of E-cadherin expression is a key event in the epithelial-mesenchymal transition. In second, part cancer cells intravasate into blood vessels and lymphatics. Inflammation promotes this with production of mediators what increase vascular permeability. In third part metastasis-initiating cells survive and travel through the circulation. Only about 0.01% of cancer cells that enter the circulation may survive and give rise to micrometastases. Integrin-mediated arrest allows the extravasation of circulating cancer cells. In part four single metastatic progenitors interact with immune, inflammatory, and stromal cells and start proliferate. One of the inflammatory signals is the extracellular matrix component versican leads to macrophage activation and production of the metastasis-promoting cytokine TNF-α. TGFβ signaling is also an important regulator of the epithelial-mesenchymal transition and metastasis. TGF β is an anti-inflammatory cytokine produced by cancer cells, myeloid cells, and T lymphocytes and if is elevated, it is a poor prognosis.Cancer cell invasion requires extensive proteolysis of the extracellular matrix at the invasive front. Inflammatory cells are important sources of proteases that degrade the extracellular matrix. In a model of invasive colon cancer, $CCR1^{+}$myeloid cells, driven by the chemokine CCL9 produced by cancer cells, promote invasiveness with secretion of the matrix metalloproteinases MMP2 and MMP9. IL-1, TNF-α, and IL-6 promote MMP expression, invasiveness, and

metastasis via NF-κB and STAT3 (Grivennikov et al.).For modeling cancer metastases spread there is several new methodologies. The nodes of a cancer metastasis network represents the distant sites where metastases could arise for a given tumor type. The size of each node represents its conditional incidence or hazard. The incidence hazard function is $h_{xmet}(t) = \frac{m_{met}(t)}{N_x(t)}$ where $m_{met}(t)$ is the number of diagnoses of metastasis met at time t and $N_x(t)$ is the number of patients remaining at time t for primary tumor type X [3]. The cumulative hazard from $X$and met pair is $H_{xmet}(t) = \sum_{t'=0}^{t} h_{xmet}(t')$ to quantify the dynamics of metastasis development, we need the incidence of metastases in terms of co-occurrence at every point of time. This allows to establish links between the primary tumor and metastasis sites, as between different metastasis sites for multiple cases.

With the fractional method as a baseline for comparison was developed an algorithm for predicting future sites of metastases using cancer metastasis networks. These networks are entities on which the metastatic disease of individual patients evolve, and are able to incorporate temporal dynamics, and subtle relational properties [4-8].

Genetic Information is not enough to Determine Whether a Cell will Become Cancerous

It is interesting to point out that the cytopathological exams indicate that the macrophage cells appear in most of treated tumors after some application session. Tumor-associated macrophages (TAM) acquire an M2 polarized phenotype represent the major inflammatory population in tumors, orchestrating various aspects of cancer, including diversion of adaptive response, cell growth, angiogenesis, matrix deposition, remodeling, construction metastasis. The existence of the closed circuit transport of ions inside of tumor promotes structural modifications in it. DC current into the tumor start an electrolytic process, where positively charged ions as (H^+, Na^+, K^+) migrate to the cathode and negatively charged ions (Cl^-) migrate to the anode. The acidity and the alkalinity together electrochemical reactions taking place in the tissue have a destructive effect over tumor. DC current changes the concentration of ions, which in turn leads to a change of the membrane potential.

There is a difference in the charge of the blood in the arteries compared to blood in the veins, i.e. there is a flow of ions along a wire is also an electromagnetic field generated around the wire. This is a network of blood vessel cables surrounded by electromagnetic fields. Probably it may be the hyaluronic acid molecules creating functional tubules inside which flow ions. The charge difference in cancer tumors may disappear when an electrical current supply achieve a charge reversal in the tumor. This charge differential is caused by the interactions of the electromagnetic fields in the body. Above circulatory network is based on spontaneously occurring electrical potentials, which are a result of metabolism and in injured or diseased tissue as a result inflammation caused torsion or necrosis. Series of experiments resulted in conclusion that fluctuating electrical potentials originating within lung masses could alter extracellular fluid dynamics. After demonstrating that electrical potentials are spontaneously generated in organs like the spleen, and potentials of this magnitude lead to formation of fibrous tissue at electrical interfaces.

Genetic information is often not enough to determine whether a cell will become cancerous; you also have to take into account the physiology of the cell and the bioelectrical signals it receives from other tissues. This has huge implications for diagnostic technology as well as our basic understanding of the role of genetics and physiology in oncology, said Michael Levin, Ph.D., Vannevar Bush Professor of Biology and corresponding author of the paper in the journal Oncotarget that describes the research [9].

Metastatic Potential Correlates with Voltage-Gated Inward Sodium Current

The afferent input from the limbic network conveys purily psychological stress reactions to the HPA axis. Due by this interplay of limbic inputs from the hippocampus, pre-frontal cortex and amygdala with the HPA axis activity evolves the vulnerable phenotype for mental illness. All cells possess long-term, steady-state voltage gradients across the plasma membrane. These transmembrane potentials arise from the activities of ion channels, pumps and gap-junctions complexes. Following studies in which multiple authors reported a decrease in the membrane potential of cells after malignant transformation. These results with observations that cultured cells under high grow conditions show a decrease in V_{mem} suggesting a causal relationship between ion flow and the cell cycle. It was also shown that sustained depolarization induce DNA synthesis and mitosis in mature neurons. The bidirectional relationship between ion transporter function and cell cycle means that this set of mechanisms are forming physiological network used during patterning to synchronize cell division. Neoplasia is associated with aberrant changes in cell cycle. Alterations in membrane potential and ion channel function were observed in many cancers. It is clear that gap junctions are important component of V_{mem}regulating its fluctuations, creating iso-potential cell fields, and modulating cellular responses to external electric fields. In human cancers hERG recruit tumor necrosis factor receptor (TNFR) to the plasma membrane causing increase in NF-κB, a known proliferation control gene. Some cancers are characterized by activation of multiple potassium currents. For example, in human melanoma lines expressing hEAG1 and Ca^{2+}-activated K^+channels. Manipulation of membrane H^+flux confers a neoplastic phenotype upon cells, and voltage-gated sodium channels potentiate breast cancer metastasis. Metastatic potential correlates with voltage-gated inward sodium current and some sodium channels may be oncofetal genes [10].

Ricci Flow Inducing DNA Damage and Genomic Instability

Activated inflammatory cells serve as sources of reactive oxigen species (ROS) and reactive nitrogen intermediates (RNI) capable by Ricci flow of inducing DNA damage and genomic instability. Probably the immune-mediated mechanisms opposed to dietary and environmental mutagens are the critical driving forces behind tumor initiation. For example, p53 mutations caused by oxidative damage, were found in both cancer cells and in inflammed, but nondysplastic epithelium in collitis associated cancer (CAC) suggesting that chronic inflammation causes genomic changes through Ricci flow. Bioelectric controls of cell functions are inherently non-linear because channels and pumps lead to effects on voltage and pH that in turn regulate those same channels and pumps.

We can model the sum of tumor promoters: (i) as membrane voltage and (j) as pH gradient like the Ricci flow. The Ricci flow equation is the evolution equation $\frac{d}{dt}g_{ij}(t) = -2R_{ij}$for a riemannian metric $g_{ij}(t)$. To understand this statement, consider a piecewise-linear mapping $f$from 2-dimensional disk into a 3-manifold, its image have self-interactions in the interior, while is not allowed have self-interactions near the boundary. Then there may exist a non-linear embedding of the disk coinciding with $f$throughout a neighborhood of the boundary. The molecular spaces with finite cyclic fundamental group, create a subfamily classified as a piecewise-linear homeomorphism using an invariant of inflammation-torsion. The topological invariant of inflammation-torsion was proved for an arbitrary simplical complex. Byproduct of this classification are knots with two bridges inR^3. The height function then has two maxima and two minima. Such a knot is uniquely determined by its associated 2-fold branched covering, which in molecular space (for example DNA). Ricci flow is then a sum of activated tumor promoters in the tumor microenvironment leading to a injury. Consider a Riemannian manifold with local coordinates$u^1, \ldots, u^n$, and with metric $ds^2 = g_{ij}du^i du^j$. The associated Ricci flow is a one parameter family of Riemannian metrics $g_{ij} = g_{ij}(t)$satisfying the differential equation $\delta g_{ij}/\delta t = -2R_{ij}$, where$R_{ij} = R_{ij}\left(\{g_{hk}\}\right)$ is the associated Ricci tensor. The Ricci tensor is essentially the only possibility. Similarly as in Einstein's theory of gravitation, we need a symmetric 2-index tensor which arises naturally from the metric tensor and its derivatives. The factor 2 in the equation is arbitrary, but the negative sign is essential. To give a simple example of the Ricci flow, consider a round sphere of radius $r$in Euclidean $(n+1)$-space. Then the metric tensor takes the form $g_{ij} = r^2 g_{ij}$ where g_{ij} is the metric for a unit sphere, while the Ricci tensor $R_{ij} = (n-1)g_{ij}$ is independent of r. The Ricci flow equation reduces to $dr^2/dt = -2(n-1)$ with solution $r^2(t) = r^2(0) - 2(n-1)t$. Thus the sphere collapses to a damage point in finite time. Suppose a start with a compact 3-dimensional manifold whose Ricci tensor is everywhere positive definite. Then, as the manifold shrinks to a point of injury under the Ricci flow, and it becomes rounder and rounder. After a finite number of Perelman "surgeries" [11] there is also one option that each component converges towards a manifold of constant positive curvature which shrinks into a point of tumor initiation in finite time. This mechanism of tumor initiation by injury as Ricci flow we can introduce through serotonin [12].

Ion Channel Drugs-"Electroceuticals"-Target the Bioelectric State of Distant Sites

The influx of mitogens like serotonin is controlled by V_{mem} through the voltage-powered serotonin membrane transporter SERT and gap-junctional paths via electrophoresis. The control of cell functions by membrane voltage is highly non-linear because of multiple feedback loops. Many of channels, pumps, and gap junctions determining transmembrane potential are themselves pH and voltage-sensitive, what is leading to complex recursion of effects. This is resulting sometimes in positive feedback loops, like NF-κB, which is turned on by K^+loss downregulating transcription of the potassium importer HK-ATPase and negative feedback loops (depolarization activate the V-ATPase hyperpolarizing pump). Quantitative mathematical modeling will be necessary to integrate the temporal dynamics of multiple ion fluxes and resulting V_{mem} changes and develop strategies for placing cells into specific V_{mem} states in biomedical applications. The non-linear and non-local aspects of bioelectric signals result in V_{mem} control over proliferation during morphogenesis. Mitotic upregulation induced by the V-ATPase is limited to the regenerating region by voltage-dependent mechanism.

Bioelectric Controls of Cell Functions are Inherently Non-Linear

Bioelectric controls of cell functions are inherently non-linear because channels and pumps lead to effects on membrane voltage and pH that in turn regulate those same channels and pumps. The V-ATPase creates both a pH gradient and contributes to membrane hyperpolarization. The HK-ATPase functions together with K^+ channel to regulate V_{mem}. Both of these components are themselves voltage-and pH-sensitive. Quantitative models of networks must take into account both the molecular biology of components expressed in relevant cells and the time-dependent physiology of the resulting circuit. For example, gating of 5-HT import/export: the epithelial cell sheet consisting of cells generate an electrical field-the physiological polarity is aligned with the cells apico-basal polarity. Neighboring cells exist in the field generated by epithelia. The field causes hyper- or hypo-polarization of a component of the cell membrane as a function of the position relative to the field axis. The overall magnitude of the membrane voltage change at a point around the cell radius at angle θ is $1.5 \cdot r \cdot E_0 \cdot \cos(\theta)$ where r is the cell radius, and E_0 is the field magnitude. The transporters are differential gated as 5-HT transporters (SERT) result in differential intracellular serotonin concentrations at the opposite poles of the cell [12].

Most confirmed tumor-promoting cytokines are M1 cytokines, but IL-10, and M2 cytokine are tumor suppressive as shown in colorectal cancer. Tumor initiation is a process when normal cells acquire the first mutational hit sending them by Ricci flow on the tumorigenic track by growth and survival advantages over their neighbors. A single mutation is insufficient and many cancers begins after four or five mutations. Each mutation is transmitted to the cell's progeny and in cancers arising within rapidly renewed epithelia. Oncogenic mutations occur in either long-lived stem cells or transient amplifying cells than within differentiated cells. They are rapidly eliminated before the next mutation strike [13]. Chronic inflammation triggered by the colonic irritant dextran sodium sulfate (DSS) induce DNA damage continuing rise to colonic adenomas.

In tumors arising in the context of inflammation or in advanced tumors with torsion-infiltrates, the effect of the immune system is stimulation of tumor growth and progression. Cancer cells representing an altered self-express non-self-antigens during stress and danger signals that promote antigen presentation. Even growing tumor is subject to immunosurveillance and killing activated T and NK cells. Immunosurveillance and tumor-promoting inflammation can coexist in the same tumor [14].

The balance between can be in favor of tumor growth. Before a tumor immune escape it may be at equilibrium [15] between tumor growth and immune destruction, during decades of tumor dormancy. The cancer cell edits its content of tumor antigens toward lower

immunogenicity and reshapes the tumor microenvironment to immunosuppressive.

These data also suggest a number of ways we might prevent, detect and treat cancer, Levin added, for example, by using ion channel drugs-"electroceuticals"-to target the bioelectric state of distant sites in the body. Ion channel agents, such as anti-epileptic drugs, are already approved for human use [16].

Earth's Magnetic Field Inhibits Growth Rates of Cancerous Lung Fibrosarcoma Cells

By understanding how the weak magnetic fields affect cancer cells and tumor growth, we can see the potential for therapy based on weak radiofrequency fields. The reduction of the Earth's magnetic field inhibits growth rates of cancerous lung fibrosarcoma cells, colorectal cancer cells and primary endothelial cells. The low-level fields modulate the production of reactive oxygen molecules, known to affect cellular proliferation and survival.

The pancreatic cancer cells show an increase in growth rate in the same low magnetic fields, indicating different cell types react differently to changes in magnetic fields. Martino has extended his work beyond cell cultures to animal models. The weak radiofrequency magnetic fields inhibit tumor growth in animal models. Further research may show the molecular mechanisms that cause different cells to react in various ways to fluctuations in static and alternating magnetic fields (FASEB, 2012).

Similar to B cells, [17] AID is overexpressed in many cancers and its expression is induced by inflammatory cytokines by NF-κB-dependent manner or by TGFβ. AID induces genomic instability and increases mutation probability during error-prone joining of double-stranded DNA breaks, introducing mutations into critical cancer genes, like Tp53, c-Myc, and Bcl-6. AID contributes to initiation of lymphomas and gastric, liver cancers. Ricci flow of inflammations-induced mutagenesis including effects of inflammation on nonhomologous recombination and NF-κB-mediated inactivation of p53 dependent genome surveillance.Epigenetic mechanisms, including microRNA-based silencing and DNA methylation, in inactivation of tumor supressors, like INK4a and APC, and changes by Ricci flow also accompanying tumor initiation. Inflammation is connected to epigenetic reprogramming by the JmjC-domain protein Jmjd3, encoded by an NF-κB target gene. Cytokines stimulate stem cell expansion so enlarging the cell pool targeted by environmental mutagens. STAT3 is linked to both stem cell reprogramming and stem cell renewal, and NF-κB can enhance Wnt/β-catenin signaling in colonic crypts. The Ricci flow connection between inflammation and tumor initiation is supported by evidence that DNA damage can lead to inflammation and promote tumorigenesis. Genotoxic stress also induce expression of NKG2D family members, serving as ligands for NK and $\gamma\delta$T cell receptors or a local inflammatory response. Mosaic deletion of the DNA repair gene ATR and Tp53 in the skin results in recruitment of $CD11b^{+}Gr1^{+}$myeloid cells, as a prototypical immune response to "altered self". Production of tumor-promoting cytokines by immune/inflammatory cells activate transcription factors, like NF-κB, STAT3, and AP-1, in premalignant cells induce genes stimulating cell proliferation and survival is a major tumor-promoting mechanism through Ricci flow. NF-κB and STAT3 activates genes controlling cell survival, proliferation, and growth, also angiogenesis, invasiveness, motility, chemokine and cytokine production. Oncogeneic transcription factors can be activated also through recognition receptors by components of bacteria and viruses. Different effects of NF-κB in changing models are determined by Ricci flow mechanism of tumor induction and the type of inflammatory response involved in tumor promotion.

Bioelectromagnetic Programming Influence Regression or Proliferation of the Cells

The life of a cell is genetically predetermined (by its reproducing capacity). Apoptosis as a programmed cell death is specific to each cell. We propose that bioelectromagnetic programming can influence either regression (apoptosis) or proliferation, regrowth and survival of the cells. Extreme local changes of pH were observed in different tumor models. Subsequently pH and voltage mediate the Ricci flow as cytotoxic effect in tumors.

Recently is there growing evidence about mechanisms converting aggression into cellular dysfunction. Various genes up-regulated by psychosocial stress are controlled by the transcription factor nuclear factor NF-κB. Metastasis is the most critical aspect of tumorigenesis mediated by the Ricci flow. Over 90% of cancer mortality is caused by metastasis [18] and requires close collaboration between cancer cells, immune, inflammatory cells, and stromal elements. Recently it is difficult to assess the overall impact of immunity and inflammation on early tumorigenic events, because direct in vivo models for evaluating the effects of these phenomena on initial tumor growth are missing.

However, it is possible to assume that tumor-promoting inflammation and antitumor immunity coexist and engage in a dynamic crosstalk at different points along the path of tumor progression and that environmental and microenvironmental factors dictate the balance between the two. What makes the same T cell subset antitumorigenic in one cancer and protumorigenic in another is not enough known and may hold the key to the development of successful immunotherapy.

NF-κB and STAT3 activate genes that control cell survival, proliferation, and growth, as well as angiogenesis, invasiveness, motility, chemokine, and cytokine production. Most likely, the diverse effects of NF-κB in different models are determined by the mechanisms of tumor induction and the type of inflammatory responses involved in tumor promotion.

Levin and Chernet, injected Xenopus laevis tadpoles with oncogenes associated with many human cancers. The oncogenes caused tumor-like structures to form in these locations. Levin and Chernet's study showed that the incidence of tumor formation could be significantly reduced through misexpression of hyperpolarizing ion channels, which control current flow across a cell membrane, even when these electrical signals originated far from the oncogene-expressing cells. "These distant bioelectric signals suppressed tumor growth, despite the cells' continued high levels of oncogene protein," said Chernet, a former doctoral student in Levin's lab.

Programming Bacteria to Prevent Tumors

Further investigation revealed that the tumor-suppressing effects of hyperpolarization were regulated by a mechanism involving the short chain fatty acid butyrate and its target, the enzyme histone deacetylase. In humans, butyrate is produced in the colon by natural bacterial fermentation of carbohydrates, and butyrate has been shown to protect against colorectal cancer. To confirm that bacterial butyrate was also involved in regulating distant tumor formation in tadpoles, the

researchers administered antibiotics; they found that the drugs indeed reduced butyrate production and thereby stopped membrane-voltage-based tumor suppression.

Their research uncovers a promising connection between the microbiome and cancer that is controlled by alterations in bioelectric signaling and also opens up exciting possibilities for biomedicine. Imagine bacteria that are metabolically programmed to produce butyrate levels appropriate to prevent tumors, said Levin.

The distance over which carcinogenesis can be predicted and controlled has been addressed in a handful of earlier studies, including work by Levin and colleagues. Levin and Chernet have shown that aberrant bioelectrical properties of tissue revealed the location where tumors were likely to form and that melanoma-like growth could be triggered by bioelectrical signaling of instructor cells far from the melanocytes. The two biologists say that more research is needed to determine whether such signaling occurs in mammalian cancer models and over what distance.

The Tufts biologists are also intrigued by the question of whether cancers emit bioelectrical information that could be detectable at a distance from the tumors themselves. "It is tempting to speculate that the long-range signaling connections are bi-directional," says Levin.

Tufts University, located on three Massachusetts campuses in Boston, Medford/Somerville and Grafton, and in Talloires, France, is recognized among the premier research universities in the USA. Tufts enjoy a global reputation for academic excellence and for the preparation of students as leaders in a wide range of professions. A growing number of innovative teaching and research initiatives span all Tufts campuses, and collaboration among the faculty and students in the undergraduate, graduate and professional programs across the university's schools is widely encouraged.

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