Essay

The Emerging Role of Voltage-Gated Ion Channels in Cancer

Minas Sakellakis * and Athanasios Chalkias

Posted Date: 5 July 2023

doi: 10.20944/preprints202307.0267.v1

Keywords: Ion; channels; regeneration; cancer; treatment; translational research; experimental research

Essay

The Emerging Role of Voltage-Gated Ion Channels in Cancer

Minas Sakellakis [1,2,*] and Athanasios Chalkias [3,4]

[1] Department of Medical Oncology, Metropolitan Hospital, 18547, Athens, Greece
[2] Department of Medicine, North Central Bronx Hospital, 10467, Bronx, USA
[3] Department of Anesthesiology, Faculty of Medicine, University of Thessaly, 41110 Biopolis, Larisa, Greece
[4] Outcomes Research Consortium, Cleveland, OH 44195, United States
* Correspondence: Department of Medicine, North Central Bronx Hospital, 3424 Kossuth Avenue, 10467, Bronx, NY, USA. Phone: +19293611558; Fax: +302104814887; Email: doctorsakellakis@gmail.com

Running Title: Ion channels modulators in cancer.

Highlights

- Elegant experiments showed that bioelectrical signals act as a top-down master regulator during embryogenesis, while electrical signals shift response to injury towards regeneration instead of healing or scarring.
- Cancer and embryogenesis not only share common phenotypical features, but also commonly upregulated molecular pathways.
- Ion channel activity is directly or indirectly linked to the pathogenesis of all cancer hallmarks, while experimental and clinical studies suggest that their modulation may exert antitumor effects.
- A large recent clinical study showed that preoperative administration of local anesthetics in patients with early breast cancer can improve survival.
- The efforts to understand and therapeutically exploit bioelectric signals in cancer should intensify.

Abstract: Preclinical evidence suggests that voltage gradients can act as a kind of top-down master regulator during embryogenesis and orchestrate downstream molecular-genetic pathways during organ regeneration or repair. Moreover, electrical stimulation shifts response to injury towards regeneration instead of healing or scarring. Cancer and embryogenesis not only share common phenotypical features, but also commonly upregulated molecular pathways. Ion channel activity is directly or indirectly linked to the pathogenesis of cancer hallmarks, while experimental and clinical studies suggest that their modulation may exert antitumor effects. A large recent clinical trial served as a proof-of-principle for the benefit of preoperative use of topical sodium channel blockade as a potential anticancer strategy against early human breast cancers. Apart from the obvious importance in perioperative medicine, it calls for the planning of further carefully designed clinical trials to expand on the concept of ion channels as tumor drivers.

Keywords: ion; channels; regeneration; cancer; treatment; translational research; experimental research

---

Introduction

Although genetic information is responsible for the synthesis of proteins during human and animal embryogenesis, it remains uncertain whether the instructions for protein-protein interactions during embryogenesis are also "hidden" in the genetic code. State-of-the-art research suggests that experimental modulation of voltage gradients induced by ion channels and pumps can orchestrate downstream molecular-genetic pathways of organ regeneration or repair, acting as a kind of top-down master regulator [1–3].

 doi:10.20944/preprints202307.0267.v1

Bioelectric signals drives embryogenesis and regeneration

In experiments conducted in *planaria* worms, Levin et al. were able to show that a bioelectrical layer, rather than genetic information, was orchestrating the regenerative patterns in the worms after amputation of large portions of their body [1]. Scientists were able to grow two different heads instead of a head and a tail, simply by using appropriate bioelectrical signals [1]. Other studies also showcased that electrical stimulation shifts response to injury towards regeneration instead of healing or scarring. Herrera-Rincon et al. reported that the use of a bioreactor device at amputated sites in adult African aquatic clawed frogs (*Xenopus laevis)* triggered a degree of regenerative response that is normally not seen [1–3].

Transcriptome analysis and RNA sequencing revealed that the bioelectrical signals altered gene expression patterns in cells at the amputation site. Genes involved in scar-tissue formation signaling and immune response were downregulated, while genes associated with oxidative stress, white blood cell activity, or serotonergic signaling were upregulated. Compared to control frogs, the ones with the device developed thicker bones, with more prominent vascularization and innervation, while their swimming patterns were closer to that of the non-amputated frogs [3]. It has also been suggested that ectopic organ formation can be triggered via appropriate manipulation of voltage gradients [4]. Moreover, experiments showed that a multi-component sleeve assembly that encompassed the amputated site, was effective in supporting the early stages in murine fingertip regeneration, when combined with electrical stimulation [5]. Several cell types exhibit galvanotaxis, while in early vertebrate embryos, electric fields not only regulate cell polarization, but can also provide important cues during cellular movement and pattern formation [6]. Experiments in zebrafish suggested that a mutation in potassium channels that affects pore formation, can alter the migration of melanosomes. Altering bioelectrical events during early embryogenesis in *Xaenopus* tadpoles may also cause melanocytes to inappropriately colonize organs or tissues [6].

In vitro studies have shown that electrical stimulation can induce cell migration, while in vivo studies suggest that osteogenesis, vasculogenesis, extracellular matrix deposition, and cell proliferation can all be increased by appropriate electric stimulation [4]. These results add to the growing body of evidence suggesting that tiny bioelectrical signals can surge among and through the cells and regulate gene expression to promote organogenesis and tissue or organ regeneration. These bioelectrical signals are the results of ion channel-induced cell polarity and voltage gradient changes [4].

Effects on cancer

Cancer is characterized by uncontrolled cellular proliferation, along with increased and inappropriate migration, apoptosis evasion, and abnormal neo-angiogenesis. Cancer and embryogenesis not only share common phenotypical features, but also commonly upregulated molecular pathways [7]. Given the similarities, it is reasonable to hypothesize that constantly altered bioelectrical signaling triggered by ion channel aberrations may be a key driver in cancer development and progression. This is also supported by the observation that specific genomic defects usually associated with cancer, sometimes do not accurately predict tumor aggressiveness, pointing towards the existence of additional drivers [8]. There is a growing body of evidence in the literature suggesting a pro-tumorigenic effect of various ion channel and pump aberrations [9]. Mutations or expression losses in ion channel genes, as well as abnormal expression/function is linked to several tumor types [10]. Ion channels are not only involved in cellular electrogenesis and excitability, but they can also form macromolecular complexes and interact with signaling molecules or adhesion proteins. In addition, they regulate cellular proliferation, differentiation, apoptosis, as well as cellular metabolism. Changes in the ion composition inside the cells affect several cellular events and molecular pathways. One notable example is cell movement which requires an ion channel-orchestrated sequence of cellular protrusions and retractions [9].

Ion channel activity is directly or indirectly involved in the pathogenesis of all cancer hallmarks, while several experimental and clinical studies suggest that their modulation may exert antitumor effects [9]. A notable example is the positive association between anesthetic drug use and increased

 doi:10.20944/preprints202307.0267.v1

overall survival in cancer patients. Potential mechanisms have been proposed, including innate and adaptive immune system modulation, or a direct effect on ion channel signaling [9]. Interestingly, local anesthetics continue to inhibit the activity and function of voltage gated sodium channels beyond the intraoperative period [9]. In a study with SW620 cell line (metastatic colon cancer), ropivacaine was found to act as a potent inhibitor of metastatic cancer cell invasion [11]. Ropivacaine was also shown to play a role in reducing prostate cancer metastatic potential, by altering intracellular ion concentration and cellular homeostasis [9]. Lidocaine and bupivacaine are other sodium channel blockers which displayed antitumor effects in experimental models [9,12,13].

A recent landmark study by Badwe et al. investigated the impact on survival of presurgical, peritumoral infiltration of lidocaine in patients with early breast cancer [14,15]. Early disease was defined as operable cancer with clinically negative or limited nodal disease and no evidence of distant metastasis. In this open-label, multicenter randomized study, 1583 patients who were not assigned to receive neoadjuvant chemotherapy received peritumoral injection of 0.5% lidocaine followed by surgery (786 patients) or surgery alone (797 patients). All patients received standard adjuvant postoperative treatments. After a median follow up of 68 months, topical lidocaine increased 5-year disease-free survival (DFS)(hazard ratio [HR]: 0.74; 95% CI: 0.58 to 0.95; p-value=0.017) and 5-year overall survival (OS) rates (HR: 0.71; 95% CI: 0.53 to 0.94; p-value=0.019). Patients who received lidocaine had an almost 4% improvement in overall survival, which is comparable to the benefit received by other current standard-of-care adjuvant interventions. The effect of topical lidocaine was similar in all the examined subgroups defined by menopausal status, tumor size, nodal infiltration status, hormone receptor status or human epidermal growth factor receptor 2 status. Moreover, the benefit was present regardless of whether the patients underwent mastectomy or removal of only the tumor and surrounding tissue. Interestingly, no adverse events accompanied lidocaine injection [14]. Despite the limitations of the study, these results are remarkable, given the lack of toxicity, the ease and low cost of intervention, and the large sample size of the trial [14].

Discussion

Preclinical evidence suggests that surgical resection of a tumor and the surgical stress response may predispose to metastasis [15]. Surgical excision can potentially modify immune function, activate neural and proinflammatory signaling, and may even induce dissemination of circulating tumor cells and increase prometastatic pathways [15]. The use of local anesthetic drugs exerts effects that can theoretically pose anticancer activity. For example, pain alleviation may decrease surgical stress response. Preclinical data have also linked lidocaine with the alteration of pathways critical for tumor cell proliferation, invasion, angiogenesis, and apoptosis evasion [15]. The study by Badwe et al. serves as a proof-of-principle for the role of sodium channel blockade as a potential anticancer strategy against human breast cancers. Apart from the obvious importance as a local treatment strategy, it calls for the planning of further carefully designed clinical trials to expand on the concept of ion channels as tumor drivers. Although local lidocaine may act more through affecting the microenvironment, a direct and long-lasting effect on tumor cells is possible. This is of particular importance because we should always consider the possibility that cancer cells have already escaped to the systemic circulation at the time of surgery. In this case (and given that sodium channel inhibition poses antitumor effects) we should not overlook the effects of systemic anesthetics by heavily shifting towards local anesthesia.

Conclusion

There is a growing body of evidence suggesting that ion channels may act as tumor drivers in several cancer types. Given their importance in human physiology, the efforts to understand bioelectric signals and ion channel blockers should intensify.

Funding: No funding received.

Acknowledgements: No acknowledgements.

Declaration of Interests: All authors report no financial or non-financial conflicts of interests.

References

1. Durant F, Morokuma J, Fields C, et al. Long-Term, Stochastic Editing of Regenerative Anatomy via Targeting Endogenous Bioelectric Gradients. *Biophys J*. 2017;112(10):2231-2243. doi: 10.1016/j.bpj.2017.04.011.
2. Oliveira KMC, Barker JH, Berezikov E, et al. Electrical stimulation shifts healing/scarring towards regeneration in a rat limb amputation model. *Sci Rep*. 2019;9(1):11433. doi: 10.1038/s41598-019-47389-w.
3. Herrera-Rincon C, Golding AS, Moran KM, et al. Brief Local Application of Progesterone via a Wearable Bioreactor Induces Long-Term Regenerative Response in Adult Xenopus Hindlimb. *Cell Rep*. 2018;25(6):1593-1609.e7. doi: 10.1016/j.celrep.2018.10.010.
4. Levin M. Reprogramming cells and tissue patterning via bioelectrical pathways: molecular mechanisms and biomedical opportunities. *Wiley Interdiscip Rev Syst Biol Med*. 2013;5(6):657-76. doi: 10.1002/wsbm.1236.
5. Hechavarria D, Dewilde A, Braunhut S, et al. BioDome regenerative sleeve for biochemical and biophysical stimulation of tissue regeneration. *Med Eng Phys*. 2010;32(9):1065-73. doi: 10.1016/j.medengphy.2010.07.010.
6. McLaughlin KA, Levin M. Bioelectric signaling in regeneration: Mechanisms of ionic controls of growth and form. *Dev Biol*. 2018;433(2):177-189. doi: 10.1016/j.ydbio.2017.08.032.
7. Manzo G. Similarities Between Embryo Development and Cancer Process Suggest New Strategies for Research and Therapy of Tumors: A New Point of View. *Front Cell Dev Biol*. 2019;7:20. doi: 10.3389/fcell.2019.00020.
8. Lee JM. The good oncogene: When bad genes identify good outcome in cancer. *Med Hypotheses*. 2011;76(2):259-63. doi: 10.1016/j.mehy.2010.10.015.
9. Sakellakis M, Chalkias A. The Role of Ion Channels in the Development and Progression of Prostate Cancer. *Mol Diagn Ther*. 2023;27(2):227-242. doi: 10.1007/s40291-022-00636-9.
10. Litan A, Langhans SA. Cancer as a channelopathy: ion channels and pumps in tumor development and progression. *Front Cell Neurosci*. 2015;9:86. doi: 10.3389/fncel.2015.00086.
11. Baptista-Hon DT, Robertson FM, Robertson GB, et al. Potent inhibition by ropivacaine of metastatic colon cancer SW620 cell invasion and NaV1.5 channel function. *Br J Anaesth*. 2014;113 Suppl 1:i39-i48. doi: 10.1093/bja/aeu104.
12. Xuan W, Zhao H, Hankin J, et al. Local anesthetic bupivacaine induced ovarian and prostate cancer apoptotic cell death and underlying mechanisms in vitro. *Sci Rep*. 2016;6:26277. doi: 10.1038/srep26277.
13. Jiang Y, Gou H, Zhu J, et al. Lidocaine inhibits the invasion and migration of TRPV6-expressing cancer cells by TRPV6 downregulation. *Oncol Lett*. 2016;12(2):1164-1170. doi: 10.3892/ol.2016.4709.
14. Badwe RA, Parmar V, Nair N, et al. Effect of Peritumoral Infiltration of Local Anesthetic Before Surgery on Survival in Early Breast Cancer. *J Clin Oncol*. 2023:JCO2201966. doi: 10.1200/JCO.22.01966.
15. Higgins T, Mittendorf EA. Peritumoral Lidocaine Injection: A Low-Cost, Easily Implemented Intervention to Improve Outcomes in Early-Stage Breast Cancer. *J Clin Oncol*. 2023:JCO2300418. doi: 10.1200/JCO.23.00418.