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Disturbance of bioelectric transmission in carcinogenesis

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Abstract

Background: Despite significant financial resources invested in the field of cancer research, there has been a steady increase in the registration of new cases of malignant neoplasms. Modern technical capabilities for analyzing the molecular substrate of tumor genesis have revealed a large number of such factors. The latest studies point out the paramount importance of the integral bioelectric field as contrasted with molecular mechanisms in oncopathology. Clear evidence has emerged that the "decision" of a certain part of the body to develop a tumor depends on the bioelectric state of remote regions. In the light of these findings, it becomes obvious that the difficulties in solving the cancer problem are associated with a simplified approach focused only on molecular components.

Conclusions: It can be assumed that the difficulties in solving the cancer problem are associated with a simplified approach, focused only on molecular components. It is difficult to identify clear differences between the blastomic and healthy cells, as they work according to the same biological principles, although differently expressed. Despite functioning with almost identical molecular components, tumor and healthy tissues differ significantly in the dynamics of growth and pattern formation. The above data indicates that the "decision" of a certain part of the body to develop a tumor depends on the bioelectric state of remote regions. In this context, the prognosis and treatment of malignant neoplasms can most likely be achieved not by local, gene-targeting technology, but by methods for the detection of tumor signatures in the morphogenetic field of the organism.

Key words: carcinogenesis, bioelectric patterns, non-coding RNAs.

Introduction

Cancer incidence is one of the most pressing problems of modern medicine. According to the International Agency for Research on Cancer GLOBOCAN, there will be an estimated 18.1 million new cancer cases (excluding 17.0 million nonmelanoma skin cancers) in 2018. Cancer is the second leading cause of death globally. The 2018 statistics show that cancer was responsible for an estimated 9.6 million deaths, and about 1 in 6 deaths was due to cancer [1]. In 2016, in the Russian Federation, the number of new registered cases of malignant neoplasms increased by 1.7% compared to 2015, and was by 20.6% higher than in 2006 [2]. Economic losses associated with this pathology are significant and are increasing each year. In 2010, the total annual economic cost of cancer diagnosis and treatment was estimated at U.S. $ 1.16 trillion [3].

Despite huge financial resources invested in the field of cancer research, the leading U.S. centers have noted a steady decline in the incidence of low-risk cancers and an absolute increase in intermediate and high-risk cancers. For instance, the proportion of low-grade prostate cancer with Gleason score 3+3 cancers decreased by 2012 from 30.2% to 17.1% in subsequent years while high-grade Gleason score 8+ cancers increased by 2012 from 6.2% to 17.5% today. At the same time, the authors note an increase by 24% in absolute numbers of GS8+ group [4].

The launch of the Human Protein Atlas ushered in a new era in the fight against cancer [5]. Decoding the human genome has become possible due to the next-generation sequencing (NGS) methods. The technology allows describing the primary structure of DNA and RNA. The main difference from earlier sequencing techniques is the possibility to "read" several sections of the genome simultaneously. A single instrument run of the NGS generates up to hundreds of megabases and gigabases of nucleotide sequence [6]. The description of the human genome has made it possible to detect abnormal behaviour of proteins in different cancers [7].

Using these technologies, Japanese researchers have identified independent oncogene panels and have compiled the first guidance for the diagnosis, treatment and prognostic evaluation of oncological diseases. The guidance describes how to use the outcomes of gene panels testing according to the type of blastomic process: childhood cancer, rare cancer, cancer of unknown primary, and cancer of unknown etiology [8].

Another facet of genetics research concerns changes of microsatellites – repetitive DNA segments (ranging in length from 1-6 or more base pairs) [9, 10]. These repeats are

found in numerous places in the genome, and have a higher mutation rate than other regions of DNA [11].

According to Wadhwa N et al. [12], a set of microsatellite markers (D9S63, D9S156, and D9S283) can be used to detect bladder cancer in high-risk population.

The most important methods for early cancer detection and prediction include identification of specific compounds circulating in the body – products of the cancerous process.

Recent studies reveal a number of RNA molecules that do not encode proteins as tumor markers. Such RNAs can be structural components of organelle (ribosomal RNA), participate in protein synthesis, (transfer RNA), have enzymatic activity, or perform regulatory functions by influencing on chromatin structure. The non-coding RNAs include: transfer RNAs (tRNA), ribosomal RNAs (rRNA), small nuclear RNAs (snRNA), small nucleolar RNA (snoRNA), antisense RNA (aRNA), micro RNA (miRNA), small interfering RNA (siRNA), piwi-interacting RNA (piRNA), long noncoding RNA (lncRNA) – Xist, Evf, Air, CTN, PINK, TUG1 [13].

These compounds can act both as oncogenes and as oncosuppressors [14, 15]. The scientists [16] have studied the effect of long non-coding RNA (lncRNA) H19 on the epithelial-mesenchymal transition (EMT) process in patients with colorectal adenocarcinoma (CRA). Genetic analysis showed that high expression of lncRNA H19 was observed in patients with poorly differentiated tumors and lymph node metastases. In the given group of patients, this indicator was also an independent predictor of adverse outcome of the disease. According to researchers, lncRNA H19 can be used as a potential biomarker for the diagnosis and treatment of colorectal adenocarcinoma.

Similar results are provided by the authors [17]. According to their opinion, overexpression of the microRNA miR-3148 promotes an increased resistance of cancer cells under conditions of hypoxia and starvation.

A comparative study of the exhaled-breath-condensate (EBC) proteome was carried out using the method of ion cyclotron resonance mass spectrometry with electrospray ionization in four donor groups: patients diagnosed with lung cancer, patients with chronic obstructive pulmonary disease, community-acquired pneumonia, and healthy nonsmokers [18]. More than 300 proteins were identified, while 19 of them were found in the EBC samples of the donors who were diagnosed with early stage lung cancer and are potentially significant in the development of a diagnostic lung-cancer biomarker panel. Thus, the EBC analysis could be a promising non-invasive method for early diagnosis of lung cancer, since the EBC protein profiles of different donor groups can be distinguished. There is a possibility of identifying a specific group of proteins inherent in a particular condition in respiratory diseases.

The use of optogenetics in the study of cell biology has increased in recent years. The method is based on the introduction of special channelopsins into the cytomembrane that respond to light excitation; channelrhodopsin was the first opsin used. Genetic engineering is applied for building of these structures [19]. Optogenetics can be used to disclose important information about signal transduction networks within cells under normal and pathological conditions [20]. Using this technology, the authors [21] have noted a change in the duration and frequency of the extracellular signal-regulated kinase (ERK) in tumor cells. In particular, blast cells that harbor particular B-Raf mutations (in the kinase P-loop) exhibit a substantially slowed kinetics of inactivation of the dynamic signal (half-time for signal decay is 10-fold longer). In these cancer cells, the active ERK output signal remains abnormally high for ~20 min compared with 1 to 2 min for normal cells.

Signal transduction is the process by which various types of signals (chemical, physical) are transmitted through a cell as a series of molecular events (most commonly protein phosphorylation), which ultimately results in a cellular response [22]. When signaling pathways interact with each other, they form networks, which allow cellular responses to be coordinated [23]. Gene activation and metabolism are examples of cellular responses to extracellular stimulation that require signal transduction. Thus, the initial impulse can activate the expression of a large number of genes, which leads to various physiological processes [24, 25].

According to the transcription process and biochemical cascades depend on the electrical potential of the cells and cell-cell interactions [26, 27, 28, 29, 30]. The electrical potential of a histiocyte is expressed by membrane voltage (Vm). The latter value is defined as the difference in electrical potential between the cytoplasm and the extracellular space [31].

The hypothesis that biological information can be transmitted by electricity was first proved in the late 1700s, when Luigi Galvani electrically stimulated muscle contraction in an amputated frog's leg [32]. Electrical properties are often associated only with excitable cells such as neurons. However, all cells possess an electrical potential across the membrane, and thus generate and receive bioelectric signals [33].

Evidence that the electric field can serve as a vector and conductor-morphogen for growth and regeneration of the soma was first provided by A.P. Matthews in 1903 when he determined the electrochemical gradient in the regenerating hydra [34]. Modern studies confirm the thesis that these voltage gradients can predict morphology, providing information on the structure, growth and formation of the organism as a whole [35, 36].

The significance of bioelectrical potential of the cell for its further differentiation and the morphogenesis of the organism is revealed by the results of researchers' experiments [37]. Using fluorescent voltage reporters CC2-DMPE and DiBAC4, bioelectric phenomena were investigated during normal development in Xenopus embryos. The images of embryos developing from gastrula to tailbud stages revealed remarkable, never-before-seen patterns of hyper′and depolarized subpopulations of visible ectodermal cells. Three courses of hyperpolarization were distinguished during the entire period of animal development. Course I was a wave that moved across the entire embryo, apparently coincident with the appearance of cilia at the blastula surface and the beginning of neurulation. Course II, being distinguished by a bright signal coming from the median ectoderm, accompanied the closure of the neural tube.

Course III represented a series of hyper-polarizations in multiple smaller areas and coincided with the change of embryonic shape from spherical to elongate. For example, the intense region of hyperpolarization of a certain group of cells marked the future stomodeum. The neighboring cells that did not contribute to this structure remained relatively depolarized.

To sum up, the authors argue that bioelectric patterns delimit the "precursor fields" – that is to say, regions within the embryo consisting of cells whose offspring will produce specific morphological features, and they can be distinguished from the neighboring cells or regions.

The results of the experiments also provide evidence that Vm is a field of morphogen that controls development at both cellular and tissue levels, and is not a simple cellular "switch" (Pai et al., 2015) [38]. The authors observed widespread apoptosis or proliferation in the adult central nervous system by the overexpression of hyperpolarizing channels in the blast cells of the frog embryo.

The electrical potential of Vm represents the long-term, slowly changing bioelectric gradient in non-excitable cells [39], and controls critical cell functions including proliferation, migration, and differentiation [40, 41]. Recent studies have also demonstrated that Vm is able to control wound healing, either directly or indirectly [42].

In the late 1960s, while studying mitotic activities in sarcoma cells, Clarence D. Cone Jr. [43] reported that Vm underwent hyperpolarization before entering M phase, and suggested that the level of Vm is correlated with cell cycle progression. Cone's theory [44] was supported by several previous studies, which demonstrated significant Vm depolarization during malignant transformation of normal cells [45, 46]. Direct *in vitro* and *in vivo* comparisons of Vm levels between normal hepatocytes and hepatocellular carcinoma cells [47], normal and neoplastic adrenocortical tissues) [48], normal embryonic fibroblasts and fibrosarcomas [49] showed that cancer cells tended to be more depolarized than their normal counterparts.

The experimental findings serve as a good example of the significance of Vm in tumor genesis [50]. Scientists induced tumor-like structures (ITLSs) in Xenopus model by overexpression of various oncogenes, such as Xrel3, Gli1, p53 (Trp248) and KrasG12D, associated with the development of melanoma, leukemia, lung cancer and rhabdomyosarcoma. Microinjection of mRNAs encoding these genes into a single blastomere resulted in clearly identifiable ITLS. The authors revealed that induced tumor-like structures (ITLSs) generated by overexpression of Xrel3 are clearly demarcated from surrounding tissue by a depolarized transmembrane potential. The unique depolarization in relation to the surrounding tissue was also observed for Gli1 and KrasG12D ITLSs. Experimental findings suggest that the depolarized transmembrane potential is a marker of ITLSs regardless of its genetic origin.

The importance of the bioelectric field as a formative one is also reported by the authors [51]. Investigating the role of bioelectric signals in embryogenesis and tumor formation by modulating chlorine channels, the Vm of individual neural crest cells were changed. These structures represent a temporary group of cells that arise from the embryonic ectoderm. The latter gives rise to multiple cell types, including melanocytes, craniofacial bones and cartilage, smooth muscle, peripheral and intestinal cells, neurons and glia [52]. During the temporary depolarization of the above embryonic cells *in vivo*, a completely different type of cells (melanocytes) acquired a phenotype similar to metastatic melanoma [51]. Melanocytes acquired dendritic morphology, increased mitotic activity, and penetrated into blood vessels and soft tissues, such as the lumen of the neural tube and brain. In addition to the appearance of this melanocyte clone, disorganization and ectopic blood vessels growth were also observed [51]. It is important to mention that the same effect was obtained using any method of depolarization of Vmem (by modulating chlorine, sodium, potassium, or hydrogen channels). This in turn indicates the primary role of a purely physiological perturbation – disturbance in Vmem in the appearance of a metastatic phenotype, and not in case of any specific gene product or ionic disturbances. Furthermore, the authors suggested that forced hyperpolarization can suppress tumorigenesis. Various hyperpolarizing ion channels and the oncogene Xrel3 were co-injected into a single blastomere of different Xenopus embryos. It has been found that hyperpolarization can prevent the formation of tumor-like structures, despite the high levels of oncogene expression in cells. The use of several different hyperpolarizing channels based on Cl– and K+ demonstrated that the suppression of neoplastic transformation is due to the Vmem hyperpolarization, and does not depend on the specificity of the ion channels.

Furthermore, scientists have complicated the experiment with the aim to identify the systemic effects of a single depolarized cell of the Xenopus embryo. One cell of embryos at the 32-cell stage was microinjected with mRNA encoding the depolarizing channel subunit KCNE1 plus mRNA encoding β-galactosidase as a lineage tracer. These embryos were then treated with the MMP-blocking compound NSC-84093, which prevents melanocytes from migrating. As a result of the experiment, despite blocking cell migration, high-dendritic melanocytes appeared in the head and on the opposite side of the experimental animal. The authors conclude that depolarized cells can exert their inductive effect at a long range, crossing the midline to affect the contralateral side. The same conclusion is confirmed by transplantation experiments: small fragments of cells from a depolarized donor transplanted into an untreated embryo induce host melanocytes to arborize and migrate inappropriately [51].

The authors [53, 54] also point to the importance of the integrity of the bioelectric field. Implanting into connective tissue of the experimental rodents rectangles of inert plastic, metal foil, or glass coverslips induces sarcomas when the material is >1 cm^2. If the material is perforated, the incidence is reduced, and the effect is not recapitulated by powders of the same material (which actually increases surface area, ruling out chemical induction or genetic damage mechanisms).

In the context of the importance of the problem concerning intercellular communication for tumor genesis and

regenerative pattern, we think it necessary to consider the early experiments of Seilern-Aspang [55]. The author described planarian experiments in which a carcinogen led to the formation of many head teratomas with irregular nerves and ectopic eyes, and concluded that "the cell-isolating action of the carcinogen prevents formation of a single morphogenetic field and leads to the establishment of several separated fields of reduced dimensions".

Consequently, it is possible that the tumor has, in some practical sense, its own bioelectric autonomous field. The latter leads to a loss of integration with the host's body layout. This phenomenon is indirectly confirmed by the fact that, in contrast to normal somatic tissues, which are reconstructed during transplantation to foreign places [56], the histopathological structure of metastasis reflects the structure of the tissue of origin rather than their destination [57].

The view that cancer is a consequence of some failure in the geometry of the organism formation is confirmed by the reversibility of the cancer process.

Thus, if intercellular communication failure leads to the formation of the tumor, then the presence of a strong formation field can presumably inhibit this pathology. This hypothesis is proved by embryo experiments, as the morphogenetic field ought to be the most active in this period. According to [58, 59], despite high malignancy and euploidy, tumor cells integrated into wild-type embryonic hosts have become integrated as normal tissue. Equally, the embryonic field present in the blastocyst can normalize several types of blastoma cells, including cells isolated from embryonic carcinoma, leukemia, and neuroblastoma [60].

According to the results of recent studies [61, 62, 63], some ion channels have been suggested as potential tumor markers. However, as previously described in the examples of experiments [51], the same effect was achieved by any method of depolarization of Vmem (by modulating -chloric, -sodium, -calcium or hydrogen channels). The researchers [64] also point out the paramount importance of the integral formation field as contrasted with molecular mechanisms at the cellular level for the integral development of an individual. The scientists' research was focused on independent methods for implementing morphogenesis. For example, renal tubules in a triton, having a constant size, can be constructed from cells of various sizes, depending on ploidy. Reaching the same macroscopic state can be realized by various underlying molecular mechanisms. Thus, the renal tubules can be formed both by bending of the cytoskeleton – twisting one very large cell around it, or by numerous small cells. The above discrepancies may, to some extent, explain the absence of a frequent direct dependence between the outcome of the cancer process and the level of tumor markers.

Despite significant efforts to identify cancer "triggers", molecular cell substrate studies have been significantly more modest. Instead of a small amount of biochemical and genetic indicators of specific blastoma cells, molecular analysis of human cancers revealed a much wider variety of such determinants [65]. As noted above, the latest studies identify a number of RNA molecules that do not encode proteins as tumor markers. According to S.A. Lavrov, et al. [66], investigated aspects of the effect of non-protein-coding RNA on chromatin structure, the actual importance of these processes at this stage turns out to be not evaluable, but, undoubtedly, enormous.

Similar conclusions can be drawn from the works of researchers [67]. The authors studied tissue and plasma samples of cancer patients treated with surgical resection using the next-generation sequencing (NGS) method. When somatic alterations identified by each test were combined, the total proportion of patients with actionable mutations increased to 71.43%. Moreover, variants of unknown significance that were assessed as likely pathogenic had a higher percentage in ctDNA exclusively.

Conclusions

Summarizing the above, it can be assumed that the difficulties in solving the cancer problem are associated with a simplified approach, focused only on molecular components. It is difficult to identify clear differences between the blastomic and healthy cells, as they work according to the same biological principles, although differently expressed. Despite functioning with almost identical molecular components, tumor and healthy tissues differ significantly in the dynamics of growth and pattern formation. The above data indicates that the "decision" of a certain part of the body to develop a tumor depends on the bioelectric state of remote regions. In this context, the prognosis and treatment of malignant neoplasms can most likely be achieved not by local, gene-targeting technology, but by methods for the detection of tumor signatures in the morphogenetic field of the organism.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
2. Kaprin AD, et al., editors. Sostoianie onkologicheskoi pomoshchi naseleniiu Rossii…v 2016 godu [The state of oncological assistance to the population of Russia ... in 2016]. Moscow; 2017. 236 p. Russian.
3. Stewart BW, Wild CP, editors. World cancer report 2014. Lyon, France: International Agency for Research on Cancer; 2014. 630 p.
4. Harrison P. Prostate cancer more aggressive in post-USPSTF era [Internet]. Medscape Medical News. 2018 August 1 [cited 2018 October 12]. Available from: https://www.medscape.com/viewarticle/900073#vp_1
5. Uhlén M, Fagerberg L, Hallström BM, et al. Proteomics. Tissue-based map of the human proteome. Science. 2015 Jan 23;347(6220):1260419.
6. Weiss GJ, Liang WS, Demeure MJ, et al. A pilot study using next-generation sequencing in advanced cancers: feasibility and challenges. PLoS One. 2013;8(10):e76438.
7. Nolting B. Noveishie metody issledovaniia biosistem [Methods in modern biophysics]. Moscow: Tekhnosfera; 2005. 254 p. Russian.
8. Sunami K, Takahashi H, Tsuchihara K, et al. Clinical practice guidance for next-generation sequencing in cancer diagnosis and treatment (Edition 1.0). Cancer Sci. 2018;109(9):2980-2985.
9. Gulcher J. Microsatellite markers for linkage and association studies. Cold Spring Harb Protoc. 2012 Apr 1;2012(4):425-432.
10. Richard GF, Kerrest A, Dujon B. Comparative genomics and molecular dynamics of DNA repeats in eukaryotes. Microbiol Mol Biol Rev. 2008;72(4):686-727.
11. Brinkmann B, Klintschar M, Neuhuber F, et al. Mutation rate in human microsatellites: influence of the structure and length of the tandem repeat. Am J of Hum Genet. 1998;62(6):1408-1415.

12. Wadhwa N, Mathew BB, Tandon S, et al. Assessment of microsatellite instability for screening bladder cancer in high-risk population. J Cancer Res Ther. 2018;14(5):916-920.
13. Lee TI, Young RA. Transcriptional regulation and its misregulation in disease. Cell. 2013;152(6):1237-1251.
14. Yoon JH, Abdelmohsen K, Gorospe M. Posttranscriptional gene regulation by long noncoding RNA. J Mol Biol. 2013;425(19):3723-3730.
15. Hung T, Chang HY. Long noncoding RNA in genome regulation: prospects and mechanisms. RNA Biology. 2010;7(5):582-585.
16. Li CF, Li YC, Wang Y, Sun LB. The effect of LncRNA H19/miR-194-5p Axis on the epithelial-mesenchymal transition of colorectal adenocarcinoma. Cell Physiol Biochem. 2018;50(1):196-213.
17. Akamine T, Morodomi Y, Harada Y, et al. miR-3148 is a novel onco-microRNA that potentiates tumor growth in vivo. Anticancer Res. 2018;38(10):5693-5701.
18. Fedorchenko KIu, Ryabokon' AM, Kononikhin AS, et al. Ranniaia diagnostika raka legkogo na osnove analiza proteoma kondensata vydykhaemogo vozdukha [Early diagnosis of lung cancer based on the analysis of exhaled-air condensate proteome].Vestnik Moskovskogo Universiteta. Seriia 2: Khimiia [Moscow University Bulletin. Series 2: Chemistry]. 2016;57(2):112-120. Russian.
19. Boyden ES, Zhang F, Bamberg E, et al. Millisecond-timescale, genetically targeted optical control of neural activity. Nat Neurosci. 2005;8(9):1263-1268.
20. Bugaj LJ, O'Donoghue GP, Lim WA. Interrogating cellular perception and decision making with optogenetic tools. J Cell Biol. 2017;216(1):25-28.
21. Bugaj LJ, Sabnis AJ, Mitchell A, et al. Cancer mutations and targeted drugs can disrupt dynamic signal encoding by the Ras-Erk pathway. Science. 2018;361(6405).
22. Bradshaw Ralph A, Dennis Edward A, editors. Handbook of cell signaling. 2nd ed. Amsterdam: Academic Press; 2010. 3048 p.
23. Papin JA, Hunter T, Palsson BO, Subramaniam S. Reconstruction of cellular signalling networks and analysis of their properties. Nat Rev Mol Cell Biol. 2005;6(2):99-111.
24. Lalli E, Sassone-Corsi P. Signal transduction and gene regulation: the nuclear response to cAMP. Journal Biol Chem. 1994;269(26):17359-17362.
25. Rosen OM. After insulin binds. Science. 1987;237(4821):1452-1458.
26. Levin M. Reprogramming cells and tissue patterning via bioelectrical pathways: molecular mechanisms and biomedical opportunities. Wiley Interdiscip Rev Syst Biol Med. 2013;5(6):657-676.
27. Accardi A. Cell signaling. Lipids link ion channels and cancer. Science. 2015 Aug 21;349(6250):789-790 .
28. Huang X, Jan LY. Targeting potassium channels in cancer. J Cell Biol. 2014;206(2):151-162.
29. Monteith GR, McAndrew D, Faddy HM, Roberts-Thomson SJ. Calcium and cancer: targeting Ca2+ transport. Nat Rev Cancer. 2007;7(7):519-530.
30. Patel F, Brackenbury WJ. Dual roles of voltage-gated sodium channels in development and cancer. Int J Dev Biol. 2015;59(7-9):357-366.
31. Levin M. Large-scale biophysics: ion flows and regeneration. Trends Cell Biol. 2007;17(6):261-270.
32. Verkhratsky A, Krishtal OA, Petersen OH. From Galvani to patch clamp: the development of electrophysiology. Pflugers Arch. 2006;453(3):233-247.
33. Levin M. Bioelectric mechanisms in regeneration: unique aspects and future perspectives. Semin Cell Dev Biol. 2009;20(5):543-556.
34. Mathews AP, Whitcher BR. Electrical polarity in the hydroids. Am J Physiol. 1903;8:294-299.
35. Tseng A, Levin M. Cracking the bioelectric code: probing endogenous ionic controls of pattern formation. Commun Integr Biol. 2013 Jan 1;6(1):e22595.
36. Adams DS, Uzel SG, Akagi J, et al. Bioelectric signalling via potassium channels: a mechanism for craniofacial dysmorphogenesis in KCNJ2-associated Andersen-Tawil Syndrome. J Physiol. 2016;594(12):3245-3270.
37. Vandenberg LN, Morrie RD, Adams DS. V′ATPase′dependent ectodermal voltage and pH regionalization are required for craniofacial morphogenesis. Dev Dyn. 2011;240(8):1889-1904.
38. Pai VP, Lemire JM, Chen Y, et al. Local and long-range endogenous resting potential gradients antagonistically regulate apoptosis and proliferation in the embryonic CNS. Int J Dev Biol. 2015;59(7-9):327-340.
39. Levin M. Molecular bioelectricity in developmental biology: new tools and recent discoveries: control of cell behavior and pattern formation by transmembrane potential gradients. Bioessays. 2012;34(3):205-217.
40. Blackiston DJ, McLaughlin KA, Levin M. Bioelectric controls of cell proliferation: ion channels, membrane voltage and the cell cycle. Cell Cycle. 2009;8(21):3527-3536.
41. Sundelacruz S, Levin M, Kaplan DL. Role of membrane potential in the regulation of cell proliferation and differentiation. Stem Cell Rev. 2009;5(3):231-246.
42. McCaig CD, Song B, Rajnicek AM. Electrical dimensions in cell science. J Cell Sci. 2009;122(Pt 23):4267-4276.
43. Cone CD Jr. Electroosmotic interactions accompanying mitosis initation in sarcoma cells in vitro. Trans N Y Acad Sci. 1969;31(4):404-427.
44. Cone CD Jr. Unified theory on the basic mechanism of normal mitotic control and oncogenesis. J Theor Biol. 1971;30(1):151-181.
45. Tokuoka S, Morioka H. The membrane potential of the human cancer and related cells. Gan. 1957;48(4):353-354.
46. Johnstone BM. Micro-electrode penetration of ascites tumour cells. Nature. 1959;183(4658):411.
47. Stevenson D, Binggeli R, Weinstein RC, et al. Relationship between cell membrane potential and natural killer cell cytolysis in human hepatocellular carcinoma cells. Cancer Res.1989;49(17):4842-4845.
48. Lymangrover J, Pearlmutter AF, Franco-Saenz R, Saffran M. Transmembrane potentials and steroidogenesis in normal and neoplastic human adrenocortical tissue. J Clin Endocrinol Metab. 1975;41(4):697-706.
49. Binggeli R, Weinstein RC. Deficits in elevating membrane potential of rat fibrosarcoma cells after cell contact. Cancer Res. 1985;45(1):235-241.
50. Chernet BT, Levin M. Transmembrane voltage potential is an essential cellular parameter for the detection and control of tumor development in a Xenopus model. Dis Model Mech. 2013;6(3):595-607.
51. Blackiston DJ, Adams DS, Lemire JM, et al. Transmembrane potential of GlyCl-expressing instructor cells induces a neoplastic-like conversion of melanocytes via a serotonergic pathway. Dis Model Mech. 2011;4(1):67-85.
52. Huang X, Saint-Jeannet JP. Induction of the neural crest and the opportunities of life on the edge. Dev Biol. 2004;275(1):1-11.
53. Oppenheimer BS, Oppenheimer ET, Stout AP. Sarcomas induced in rodents by imbedding various plastic films. Proc Soc Exp Biol Med. 1952;79(3):366-369.
54. Bischoff F, Bryson G. Carcinogenesis through solid state surfaces. Prog Exp Tumor Res. 1964;5:85-133.
55. Seilern-Aspang F, Kratochwill L. Relation between regeneration and tumor growth. In: Kiortsis V, Trampusch H, editors. Regeneration in animals and related problems. Amsterdam: North-Holland Publishing Company; 1965. p. 452-73.
56. Farinella-Ferruzza N. The transformation of a tail into a limb after xenoplastic transformation. Experientia. 1956;15:304-305.
57. Tarin D. Cell and tissue interactions in carcinogenesis and metastasis and their clinical significance. Semin Cancer Biol. 2011;21(2):72-82.
58. Mintz B, Illmensee K. Normal genetically mosaic mice produced from malignant teratocarcinoma cells. Proc Natl Acad Sci USA. 1975;72(9):3585-3589.
59. Li L, Connelly MC, Wetmore C, et al. Mouse embryos cloned from brain tumors. Cancer Res. 2003;63(11):2733-2736.
60. Pierce GB, Pantazis CG, Caldwell JE,Wells RS. Specificity of the control of tumor formation by the blastocyst. Cancer Res. 1982;42(3):1082-1087.
61. Voloshyna I, Besana A, Castillo M, et al.TREK-1 is a novel molecular target in prostate cancer. Cancer Res. 2008;68(4):1197-1203.
62. Diss JK, Stewart D, Pani F, et al. A potential novel marker for human prostate cancer: voltage-gated sodium channel expression in vivo. Prostate Cancer Prostatic Dis. 2005;8(3):266-273.
63. Zhiqi S, Soltani MH, Bhat KM, et al. Human melastatin 1 (TRPM1) is regulated by MITF and produces multiple polypeptide isoforms in melanocytes and melanoma. Melanoma Res. 2004;14(6):509-516.
64. Fankhauser G. Maintenance of normal structure in heteroploid salamander larvae, through compensation of changes in cell size by adjustment of cell number and cell shape. J Exp Zool. 1945;100:445-455.
65. Hahn WC, Weinberg RA. Rules for making human tumor cells. N Engl J Med. 2002;347(20):1593-1603.
66. Lavrov SA, Kibanov MV. Nekodiruiushchie RNK i struktura khromatina [Noncoding RNA and chromatin structure]. Uspekhi Biologicheskoy Khimii [Biological Chemistry Reviews] (Moscow). 2007;47:53-88. Russian.
67. Chang YS, Fang HY, Hung YC, et al. Correlation of genomic alterations between tumor tissue and circulating tumor DNA by next-generation sequencing. J Cancer Res Clin Oncol. 2018;144(11):2167-2175.