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Do drugs that inhibit voltage-dependent sodium channels have a role in the treatment of cancer?

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Τα φάρμακα που αναστέλλουν τα εξαρτώμενα από την τάση κανάλια νατρίου διαδραματίζουν κάποιον ρόλο στη θεραπευτική αντιμετώπιση του καρκίνου;

Περίληψη στο τέλος του άρθρου

Key words: Cancer, Treatment, Voltage-dependent sodium channels

Cancer is increasingly prevalent and is one of the leading causes of death in the world and constitutes a major problem of public health. Although early diagnosis of the disease significantly reduces the mortality, the treatment methods are often inadequate when the disease progresses. It is therefore important to know the mechanism of the molecular changes that underlie the transformation of normal into cancerous cells and cause them to metastasize.

In the past decade it has become clear that ion channels are vitally important in tumor development and in the growth and spread of cancer. During the transformation of a normal cell into a cancer cell, a series of genetic alterations may occur which affect the expression of ion channels or cause a change in ion channel activity. Ion channels are associated with proliferation, apoptosis, migration, angiogenesis and metastasis of cancer cells.[1–4]

Ion channels in the plasma membrane are located within the basic structural elements of all living cells and are required for cell proliferation. Ion channels are macromolecular protein complexes that cut the lipid bilayer of the membrane and facilitate the movement of ions through this layer. These channels allow the passage of ions through the cell membrane under the influence of various different parameters, including membrane lipids, the intracellular and extracellular pH, mechanical stress, membrane voltage and the electrochemical ion gradient.

Ion channels also play an important role in regulating the cellular ion balance. There are two major subclasses of ligands (neurotransmitters) with gates and voltage gates. Voltage-gated ion channels are members of a large gene family, many of which are opened in response to membrane depolarization and are highly dependent on voltage. The ion channels in this class are the voltage gated Na(+) and K(+) channels. Voltage dependent sodium channels (VGSC) play a role in the action potential in many physiological processes, including signal transduction in neurons, muscle contraction, hormone release, cardiac pacing and neurotransmitter release.[2–4]

Studies have shown that VGSC is associated with many pathophysiological conditions, including cancer. In particular, gene expressions of voltage-gated ion channels permeable to sodium ions are significantly increased in most cancer cells.[1–3] In a number of human carcinomas, including breast, prostate, lung and cervix cancer, and lymphoma, mesothelioma, neuroblastoma and melanoma, expression of VGSCs is reported to be increased under both *in vivo* and *in vitro* conditions. In addition, VGSCs have been associated with an increase in metastatic cancer cell lines and there is increased expression and activity of VGSC in metastatic breast, prostate and cervical carcinoma biopsies. In addition, the activity of VGSC has been shown to promote cell motility, endocytosis and invasion.[1,2]

One of the main problems and difficulties in the treatment of cancer is multiple drug resistance to chemotherapy. Attempts, therefore, are being made to increase the effectiveness of existing drugs. Among the different mechanisms involved in the development of drug resistance in cancer

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cells, changes in the expression of ion channels are known to cause drug resistance.[4] In the review of Arcangeli and Becchetti, studies are cited that show that the pumps with voltage-gated Na channels play a role in chemotherapeutic drug resistance.[5]

Promising data suggest that VGSC can be considered a new therapeutic target in cancer treatment. Specific drugs that may regulate the function of VGSCs and show their pharmacological effects as channel blockers include local anesthetics such as lidocaine, and antiepileptic drugs, such as lamotrigine, carbamazepine and phenytoin.[1–4] Antiepileptic drugs capable of blocking VGSCs, including phenytoin and carbamazepine, have been shown to inhibit proliferation in human prostate cancer cell lines.[6] Phenytoin has been shown to suppress both Na (+) current and metastatic cell behaviors, such as migration and invasion, in metastatic breast cancer cells by acting on the Nav 1.5 subtype.[7] Lidocaine, a local anesthetic, has been shown to suppress endocytic activity in small cell lung cancer cells.[8]

VGSC plays a role in many physiological and pathological processes, including signal transduction, muscle contraction, hormone secretion, tumor development, cancer growth and chemotherapeutic drug resistance in neurons and studies show that this could provide the basis for effective treatment.

ΠΕΡΙΛΗΨΗ

Τα φάρμακα που αναστέλλουν τα εξαρτώμενα από την τάση κανάλια νατρίου διαδραματίζουν κάποιον ρόλο στη θεραπευτική αντιμετώπιση του καρκίνου;

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Τα κανάλια νατρίου που εξαρτώνται από την τάση διαδραματίζουν κάποιον ρόλο στις φυσιολογικές και στις παθολογικές διεργασίες, όπως η μεταγωγή σήματος, η σύσπαση των μυών, η έκκριση ορμονών, η εμφάνιση όγκων, η ανάπτυξη καρκίνου και η αντίσταση σε χημειοθεραπευτικά φάρμακα στους νευρώνες. Υπάρχουν διάφορες μελέτες που δείχνουν ότι μπορεί να αποτελούν μια αποτελεσματική θεραπεία. Ωστόσο, είναι απαραίτητο να διευκρινιστεί ο ρόλος των ασθενών στη θεραπεία.

Λέξεις ευρετηρίου: Θεραπεία, Κανάλια νατρίου, Καρκίνος

References

1. BOUZA AA, ISOM LL. Voltage-gated sodium channel β subunits and their related diseases. *Handb Exp Pharmacol* 2018, 246:423–450
2. RHANA P, TRIVELATO RR Jr, BEIRÃO PSL, CRUZ JS, RODRIGUES ALP. Is there a role for voltage-gated Na+ channels in the aggressiveness of breast cancer? *Braz J Med Biol Res* 2017, 50:e6011
3. MARTIN F, UFODIAMA C, WATT I, BLAND M, BRACKENBURY WJ. Therapeutic value of voltage-gated sodium channel inhibitors in breast, colorectal, and prostate cancer: A systematic review. *Front Pharmacol* 2015, 6:273
4. HOFFMANN EK, LAMBERT IH. Ion channels and transporters in the development of drug resistance in cancer cells. *Philos Trans R Soc Lond B Biol Sci* 2014, 369:20130109
5. ARCANGELI A, BECCHETTI A. New trends in cancer therapy: Targeting ion channels and transporters. *Pharmaceuticals (Basel)* 2010, 3:1202–1224
6. ABDUL M, HOOSEIN N. Voltage-gated sodium ion channels in prostate cancer: Expression and activity. *Anticancer Res* 2002, 22:1727–1730
7. YANG M, KOZMINSKI DJ, WOLD LA, MODAK R, CALHOUN JD, ISOM LL ET AL. Therapeutic potential for phenytoin: Targeting Na(v)1.5 sodium channels to reduce migration and invasion in metastatic breast cancer. *Breast Cancer Res Treat* 2012, 134:603–615
8. ONGANER PU, DJAMGOZ MB. Small-cell lung cancer (human): Potentiation of endocytic membrane activity by voltage-gated Na(+) channel expression *in vitro*. *J Membr Biol* 2005, 204:67–75

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