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Review

Targeting ion channels for cancer therapy by repurposing the approved drugs☆

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ABSTRACT

Ion channels have been shown to be involved in oncogenesis and efforts are being poured in to target the ion channels. There are many clinically approved drugs with ion channels as "off" targets. The question is, can these drugs be repurposed to inhibit ion channels for cancer treatment? Repurposing of drugs will not only save investors' money but also result in safer drugs for cancer patients. Advanced bioinformatics techniques and availability of a plethora of open access data on FDA approved drugs for various indications and omics data of large number of cancer types give a ray of hope to look for possibility of repurposing those drugs for cancer treatment. This article is part of a Special Issue entitled: Membrane channels and transporters in cancers.

Contents

1. Introduction

Cancer is the second most common cause of deaths in the United States [1]. Cancer is characterized by sustained proliferation, resistance to cell death, evasion of growth suppressors, angiogenesis, gain of metastatic properties, and replicative immortality. These are famously called as hallmarks of cancer [2], additional two being evasion of immune system and reprograming of cell metabolism [3]. During the process of acquisition of these hallmarks cancer cells exploit a variety of normal cellular signaling mechanisms and use functionally diverse proteins. Amongst those, few are well studied while others are not. Our understanding about the role of one such class of proteins called membrane channels is in infancy. But available data strongly suggest the critical role of membrane channels in cancer pathophysiology (for detailed reviews refer [4,5]).

The role of ion channels in specialized excitable cells like neurons and cardiac myocytes is very well known. Involvement of ion channels

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in pathophysiology of various diseases/disorders has been studied and drugs have been developed to cure those diseases. But an interest to study the role of these channels in cancer pathophysiology was triggered by seminal studies delineating the role of K^+ channels in mitogenesis [6] and oncogenesis [7]. This stimulated the search for possibility of targeting these ion channels to treat cancer [8–10]. Eventually the ion channels became a point of discussion as a drug target culminating into a special colloquium on "Ion channels and Cancer" in 2007 [11]. Ion channels play critical roles in cancer pathophysiology by several mechanisms. Ion channels like Ca^{2+}, and Na^+/K^+ control cancer cell proliferation by regulating several key survival signaling pathways and membrane potential. A cancer cell undergoes changes in the cell volume while progressing through various phases of cell cycle. Cell volume is mainly regulated by ions like potassium, calcium, sodium and chloride. During migration, cancer cells use water current to propel their body in confined spaces [12]. Various ion channels along with aquaporin play an important role in manipulating movement of water molecules across the cell which propels the cells forward. This mechanism is explained by the 'osmotic engine model' [12]. As per this model, during cell migration NHE-1 (Na^+/H^+ exchanger-1) and AQP5 (aquaporin 5) are polarized at the leading edge. By using these ion channels, cells allow in-flow of water at the leading edge and out-flow at the trailing edge. This net turnover of water generates propulsive force resulting into net displacement of the cell [12].

Readers can find detailed roles of various ion channels in cancer pathophysiology elsewhere in this issue. We have summarized roles of various ion channels in hallmarks of cancer and various tumors in Tables 1 and 2. Despite their importance in cancer, there are hardly any drugs designed specifically to target ion channels as cancer therapeutics. There are many drugs primarily used to treat diseases like hypertension, psychiatric disorders which are also inhibitors of ion channels with different potency. These clinically approved drugs can be repurposed for cancer indication which will save time and significant amount of money. Also these drugs are in the clinic for a long period of time with known safety profile.

Repurposing of the approved drugs has many benefits in its basket to offer such as:

1. Known safety profile
2. Well understood pharmacokinetics in humans
3. Reduced time to repurpose the candidate from 10–17 years to 3–12 years [14]
4. Cost effectiveness. Can save large amount of money being spent on early development
5. Since closer to the market authorization, easy to attract venture capitalist to invest.

In general there are several different options for repurposing the existing approved drugs [15]: A) Disease based approach is suitable when we have very good information about pathogenesis (with omics data) of a particular cancer. With omics information about the particular cancer the FDA-approved drugs can be screened in silico to target the key pathways: e.g. sunitinib for metastatic breast cancer. B) When we have little information about a cancer type, FDA-off label screening is a suitable method: e.g. rituximab for breast cancer. C) If we have omics information about a particular drug (i.e. target information about a drug), the drugs can be screened in relevant cancers with dysregulation of those proteins: e.g. sirolimus for patients with dexamethasone-resistant acute lymphoblastic leukemia. D) If we have information of key protein/s in a cancer, FDA-approved drugs can be screened for that particular target/s. Amongst these approaches, the later two seem to be the most suitable for repurposing the drugs as ion channel inhibitors (Fig. 1). However, not necessarily these approaches will be explored in isolation. Sometimes with available data, more efficient combined approaches may be taken. Jahchan et al. demonstrated the effective way to identify existing FDA approved drugs for new indications [16]. They used bioinformatics tools to identify potential candidate drugs for the treatment of small-cell lung cancer (SCLC) from publicly available database of FDA approved drugs. They finally narrowed down to a class of anti-psychotic drugs and identified

Table 1
Involvement of ion channels in hallmarks of cancer and potential therapeutic agents.

Hallmarks of cancer	Membrane channels/transporters involved	References
Cell growth	1. Cys-loop, cationic Ca^{2+} permeable: nAChR α7 (I)	[121]
	2. Voltage gated Ca^{2+} (Ca_v): Ca_v1 L-type (I), $Ca_v2.3$ R-type (I), $Ca_v3.2$ T-type (I)	[86,92,94–97,99,122]
	3. Voltage gated K^+ (K_v): $K_v10.1$ (I), $K_v11.1$ (I), $K_v1.3$ (I)	[7,22–26]
	4. Ca^{2+} activated K^+ (K_{Ca}): $K_{Ca}3.1$	[24]
	5. Inwardly rectifying K^+ (K_{ir}): $K_{ir}3.1$ (I), $K_{ir}6.1$ (I)	[27–30]
	6. Background K^+ (K_{2P}): $K_{2P}2.1$ (I), $K_{2P}9.1$ (I)	[31,32]
	7. TRP: TRPC6 (I), TRPV6 (I), TRPM7 (I)	[123–125]
Insensitivity to antigrowth signals	1. Purinergic, cationic Ca^{2+} permeable: $P2X_{5/11}$ (D)	[126,127]
	2. Voltage gated K^+ (K_v): $K_v11.1$ (I)	[25]
	3. Ca^{2+} activated K^+ (K_{Ca}): $K_{Ca}1.1$	[33]
	5. TRP, cationic Ca^{2+} permeable: TRPC1, TRPC4 (D)	[123,128]
Evasion of apoptosis	3. Background K^+ (K_{2P}): $K_{2P}9.1$ (D)	[34]
	4. SOC, Ca^{2+} selective: Orai1 (D)	[129,130]
	5. TRP, cationic Ca^{2+} permeable: TRPV6 (D), TRPM2 (D)	[131,132]
	6. Cl^- channels: CIC-3 (I)	[133–136]
Limitless replicative potential	1. Voltage gated Ca^{2+} (Ca_v): Ca_v1 (L-type) (I)	[137]
Angiogenesis	1. Voltage gated K^+ (K_v): $K_v10.1$ (I), $K_v11.1$ (I)	[35]
	2. Ca^{2+} activated K^+ (K_{Ca}): $K_{Ca}1.1$ and $K_{Ca}3.1$ (I)	[36–38]
	3. SOC, Ca^{2+} selective: Orai1 (I)	[138]
	4. TRP, cationic Ca^{2+} permeable: TRPC3 (I), TRPC4 (I), TRPC6 (I)	[139–141]
Metastasis	1. Voltage gated Na^+ (Na_v): Nav1.5 (I), Nav1.7 (I)	[142,143]
	2. Voltage gated Ca^{2+} (Ca_v): $Ca_v3.1$ (I)	[98]
	3. Voltage gated K^+ (K_v): $K_v11.1$ (I)	[39]
	4. Ca^{2+} activated K^+ (K_{Ca}): $K_{Ca}1.1$ (I), $K_{Ca}2.3$ (I), $K_{Ca}3.1$ (I)	[40–43]
	5. Inwardly rectifying K^+ (K_{ir}): $K_{ir}3.1$	[27]
	6. SOC, Ca^{2+} selective: Orai1 (I)	[144]
	7. TRP, cationic Ca^{2+} permeable: TRPC1 (I)	[145]
	8. TRP, cationic Ca^{2+} permeable: TRPM1 (D)	[146]
	9. Na^+ non-voltage-gated, DEG-related: ENaCα, ENaCγ, ASIC1 (I), ASIC2 (D)	[147,148]
	10. Cl^- channels: CIC-3 (I)	[40]

Channel names are in IUPHAR nomenclature; I—increase; D—decrease.