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Review

Oncochannels

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ABSTRACT

A hallmark of tumour cells is an aberrant expression of ion channels. Research of the recent years clearly indicates that the change in the "channelome" that accompanies tumourigenesis is not just an epiphenomenon of neoplastic transformation. This is deduced from the fact that experimental interference with the channelome often impairs survival, proliferation, malignant progression, invasive behaviour, or therapy resistance of the tumour cells. Rather, the channelome of the tumour cell does induce onogenic processes and keeps them running. The involved ion channels are often overexpressed in several tumour entities suggesting their high oncogenic potency. The present review article aims to summarize our current knowledge on these "oncochannels", how they crosstalk within the signalling of a tumour cell and how they exert their oncogenic function.

1. Introduction

Traditionally, ion channels are within the research area of biophysicists and physiologists, who developed the required recording methodology to assess channel function in order to address primarily physiological issues. As a result of these efforts, function and regulation of ion channels in physiological processes such as epithelial transports or excitability are increasingly understood. Over the recent years, however, overwhelming pieces of evidence are accumulating that argue for ion channel functions beyond those described by classical physiology. More and more, it turns out that virtually all cellular processes rely on ion channels. By modifying the chemistry, electricity and mechanics of every cell, ion channels seem to have a plethora of tools to regulate the activities of downstream effectors molecules, to modify epigenetics [1], and gene expression [2]. In addition, recent observations suggest that ion channels may signal via direct molecular interaction in macromolecular complexes [3], or even as transcription factor [4]. Hence, ion channels may impact on cell biology in a manifold and highly complex manner. This complexity is one reason why data on the signalling functions of ion channels often remain on a phenomenological level.

Searching in Pubmed for "ion channels AND cancer" retrieves several thousands articles often in highly prestigious journals hinting to both, the growing scientific attention to ion channels in cancer research and the functional significance of ion channels in tumour biology. As thematized in this article, aberrant ion channel expression has been shown for many tumour entities. Most importantly, the altered channelome in tumour cells has been demonstrated to contribute actively to neoplastic transformation, malignant progression, adaptation to the tumour microenvironment, metastasis, or resistance to anticancer therapy. The mechanisms, underlying the control of these processes by ion channels are – because of the above mentioned reasons – often not defined. Unlike oncogenes, ion channels have not been reported to initiate neoplastic transformation of cells. Rather, they are drivers of the oncogenic processes by adjusting an oncogenic Ca^{2+} signature, membrane voltage, Na^{+} concentration, pH, etc. In line with this assumption are the observations that experimental interference with ion channel function often impairs tumour cell growth or survival, "outing" the ion channels as "oncochannels".

An important further reason for the study of oncochannels is the possible translation of the acquired knowledge into anti-cancer therapy. Many pharmacological ion channel modulators are already in clinical use or currently tested in clinical trials [5]. In addition, some oncochannels are highly over-expressed in tumours, qualifying them as possible tumour-associated antigens for anti-tumour vaccination trials [6]. Moreover, oncochannel overexpression together with their plasma membrane location makes the specific targeting of tumour cells feasible using oncochannel-specific

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antibodies as vehicle [7]. Clinical trials or mouse models have already proven the different concepts of targeting oncochannels [8]. This review article aims to provide a summary of what is known about the role of ion channels in tumour suppression, neoplastic transformation and malignant progression, as well as tumour cell migration and invasion, and therapy resistance. To begin with, possible mechanisms of signalling by oncochannels will be discussed.

2. Signalling by oncochannels

Considering the oncogenic potential of ion channels, the most intriguing question is, how channel activity may crosstalk with the biochemical signalling and interfere with tumour cell biology. Besides the most obvious mechanism, the modulation of the Ca^{2+} signalling, ion channels have turned out to regulate the cell behaviour via multiple ways as discussed in the following paragraphs.

2.1. Macromolecular signalling complexes

An example for an ion channel highly up-regulated in many tumour entities is the human voltage-gated ether-à-go-go-related (hERG) K^+ channel [9–14]. hERG has been demonstrated predominantly by the pioneering work of Annarosa Arcangeli's group in Florence, Italy, to accomplish outside-in signalling. hERG channels build macromolecular signalling complexes with beta1 integrin, VEGF receptor and/or CXC chemokine receptor-4 in the plasma membrane of leukaemia [15,16] and neuroblastoma cells [12] (Fig. 1). It has been shown that hERG channel activity bridges beta1 integrin binding to extracellular matrix proteins to downstream signalling pathways such as ERK1/2, PI3K/Akt or Rac1/FAK pathways by conformational coupling rather than by K^+ fluxes [12,15–17]. Importantly, hERG blockade attenuates beta1 integrin

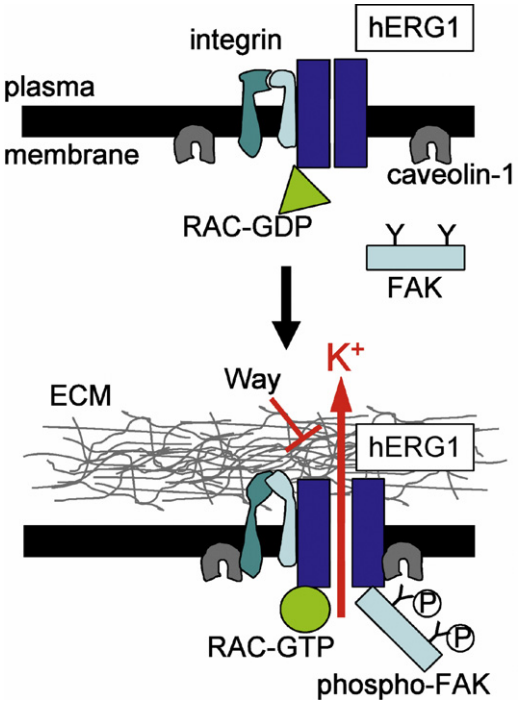

Fig. 1. hERG channels build macromolecular signalling complexes with beta1 integrin. hERG channel activity bridges beta1 integrin adhesion to fibronectin to downstream signalling molecules such as focal adhesion kinase (FAK) or the small GTPase Rac1. Inhibition of hERG with its specific blocker Way 123,398 prevents tyrosin phosphorylation of FAK and activation of Rac1 induced by fibronectin-integrin binding [12].

signalling. In addition, plasmalemmal hERG1/beta1-integrin complexes seem to be specific for cancer cells [17]. Together, this makes hERG1 an attractive pharmacological target for anti-cancer therapy. *In vivo* studies in immunocompromized mice have proven such a therapy concept: hERG1 channel blockade indeed reduced leukaemic infiltration, increased survival of the mice and enhanced the therapeutic effect of corticosteroids [16]. Hence, targeting oncogenic signalling complexes harbouring hERG1 seems to be a promising clinical therapy strategy provided that the cancer cells express hERG1 splice variants other than those mediating repolarization of the heart action potential and that isoform-specific drugs are available.

Ether-à-go-go (EAG1) voltage-gated K^+ channels are closely related to hERG1 and are expressed in brain and in many tumour entities [18,19]. Transfection of non-transformed cells with EAG1 stimulates cell proliferation via the p38 MAPK pathway indicating the high oncogenic potential of EAG1 [20]. Notably, data on non-conducting mutants indicate that this signalling is independent of EAG1-mediated ion-fluxes but dependent on conformational changes of the EAG1 voltage sensor [20]. This suggests that EAG1, like hERG1, signals in macromolecular complexes via direct protein-protein interaction. Such interaction has been demonstrated in Drosophila, where EAG binds to Ca^{2+}/calmodulin (CaM)-dependent kinase II (CaMKII) and sustains its kinase activity [21]. In summary, voltage-gated K^+ channels such as EAG1 or hERG1 may signal via direct protein-protein interaction possibly through voltage-gated conformational changes. Changes of the membrane voltage might also modulate proteins other than ion channels as introduced in the next paragraph.

2.2. Electrosignaling

By modifying the voltage across membranes, ion channels generate electrical signals which regulate, for instance, the Ca^{2+} signalling via voltage-dependent Ca^{2+} entry, -release and extrusion pathways. Beyond that, electrosignals may directly translate into biochemical signalling. As an exceptional example, voltage-sensing phosphatases (VSPs) are depolarization-activated phosphoinositide-phosphatases. VSPs, which were first described in the sea squirt *Ciona intestinalis* [22]. They are also expressed in mammals. Whether human orthologs like mouse VSPs are electrically active remains to be defined [23]. In addition to direct voltage regulation, recruitment of signalling molecules to the membranes may be dependent on the membrane voltage. For instance, the translocation to the inner mitochondrial membrane and the consecutive degradation of the kinase PINK1 have been demonstrated to require high voltage ($\Delta\Psi_m$) across the inner mitochondrial membrane. Dissipation of $\Delta\Psi_m$ in damaged mitochondria prevents PINK degradation and induces mitophagy [24,25]. Finally, all electrogenic transports with their accompanying H_2O fluxes and concurrent cell volume changes depend on voltage. As a consequence, electrosignaling of ion channels is directly linked to chemical signalling.

2.3. Chemical signalling

Signal- or effector proteins may be modified by physiological and pathophysiologicgal changes in the intracellular ion activities. Execution of apoptotic cell death requires K^+ channel-mediated decrease in intracellular K^+ concentration since apoptosome formation, caspases and nucleases are inhibited by high cytosolic K^+ concentrations [26]. Furthermore, acidic or basic amino acid residues within their specific molecular environment (i.e., electrostatic interactions and solvent accessibility) may adopt pKa values that are close to the physiological intracellular or extracellular pH. As a consequence, small changes in intracellular or extracellular pH