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INVITED REVIEW

Ion channels in sarcoma: pathophysiology and treatment options

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Abstract

Sarcomas are characterized by aggressive growth and a high metastasis potentially leading in most cases to a lethal outcome. These malignant tumors of the connective tissue have a high heterogeneity with numerous genetic mutations resulting in more than 100 types of sarcoma that can be grouped into two main kinds: soft tissue sarcoma and bone sarcoma. Sarcomas are often diagnosed at late disease stage, whereas a guaranteed diagnosis of the sarcoma type is fundamental for successful therapy. However, there is no appropriate therapy available. Therefore, the need for new therapies, which prolong survival and improve quality of life, is high. In the last two decades, the role of ion channels in cancer has emerged. Ion channels seem to be an ideal target for anti-tumor therapies. However, different cancer types have their own altered ion channel pattern, and the knowledge about the tumor-associated ion channel expression is fundamental. Here, we focus on the role of different ion channels in sarcoma, their pathophysiology, and possible treatment options.

Keywords Ion channels · Cancer · Tumor · Sarcoma · Soft tissue sarcoma · Bone sarcoma

Introduction

Sarcomas are characterized by aggressive growth and a high metastasis potentially leading in most cases to a lethal outcome. These malignant tumors of the connective tissue have a high heterogeneity with numerous genetic mutations resulting in more than 100 sub-classifications [12, 13, 58]. These tumors account for 11 % of child cancer types. Sarcoma arises from mutated cells of mesenchymal origin (fat, muscle, bone, cartilage, vascular, or hematopoietic tissue), all sharing certain microscopic characteristics and similar symptoms [52]. Given by this diversity of possible origin, there are many subtypes of sarcoma, which are classified, based on their histological patterns and molecular signatures [56]. Although sarcomas have relatively low incidence rates, the disease often takes a fatal clinical course. This is due to unspecific clinical symptomatic or no symptomatic at all in early disease stages. Moreover, you need specialized sarcoma centers for the molecular diagnosis of sarcomas. Another important aspect to mention is that treatments in specialized sarcoma centers show a significantly better overall survival [10, 11].

Sarcomas are divided in the two main groups of (1) bone sarcomas (including osteosarcoma, Ewing's sarcoma, and chondrosarcoma), accounting for around 10 % of all sarcomas, and (2) soft tissue sarcomas (including, e.g., liposarcoma, fibrosarcoma, synovial cell sarcoma, rhabdomyosarcomas, gastrointestinal stromal tumor (GIST)) that form the vast majority of all diagnosed sarcoma [13]. Sarcomas are further sub-classified based on the type of presumed cell of origin found in the tumor. So far, there is no promising drug therapy available for sarcomas. Therefore, it is of highest interest to gain a better understanding about the tumor diversities, tumor microenvironment, and the mechanisms underlying the development of these cancers.

Ion channels have emerged as relevant players in the cross-talk between tumor cells and their tumor microenvironment and as potential targets because of the following aspects [2]:

1) Ion channels play an important role in cancer biology (proliferation, angiogenesis, differentiation, apoptosis) (Fig. 1).
2) Ion channels are expressed at the cell surface as well as in different cellular components of the tumor microenvironment.
3) There are often pharmacological tools available to modulate ion channel activity.

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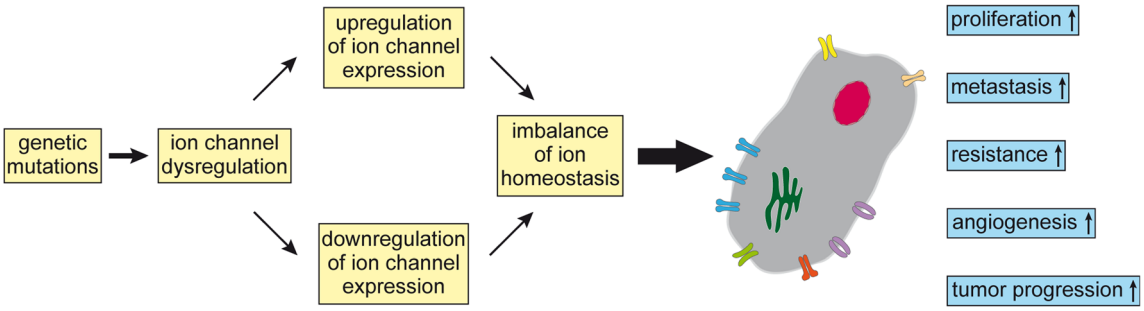

Fig. 1 Contribution of ion channel dysregulation to characteristic cancer properties

Ion transport across the cell membrane is critically important for the hallmarks of cancer, a set of six acquired functional capabilities of cancers defined by Hanahan and Weinberg, namely self-sufficiency in growth signals, insensitivity to growth-inhibitory (antigrowth) signals, evasion of programmed cell death (apoptosis), limitless replicative potential, sustained angiogenesis, and tissue invasion and metastasis [30]. Compared to their origin cell, cancer cells often show a modified cancer-related ion channel expression pattern; in most cases, a significant increase in their abundance. This is even more manifest in tumor stem cells, which are more resistant to cancer therapies. Ion channels seem to be an ideal target for anti-tumor therapies. However, different cancer types have their own altered ion channel pattern and the knowledge about the tumor-associated ion channel expression is fundamental [40, 53]. In the following, we will focus on the role of different ion channels in sarcoma (Fig. 2; Table 1).

Ion channels in sarcoma

Ion channels are integral membrane proteins allowing the passive passage of ions into or out of a cell along their electrochemical gradient [34]. Ion channels themselves are able to open and close as a response to specific regulatory signals or as a reaction to different chemical or physical stimuli. The channels can be classified according to the gating stimulus or the nature of the ion species they let pass. Ion channels have the ability to interfere in a plethora of cell processes by using their tools of fine-tuning the chemistry, electricity, and mechanics of cells.

Voltage-gated K^+ channels (K_V)

Voltage-gated K^+ channels comprise a large, ubiquitously expressed transmembrane protein family activated by changes in the electrical membrane potential. For humans, 40 voltage-gated potassium channel genes, grouped in 12 subfamilies, have been described [28]. According to sequence similarities and function, the family of voltage-dependent potassium channels can be divided into several subfamilies. One family of K_V channels is the shaker-related subfamily (K_V1). It is named after the founding member of the family identified in "shaker" mutants of *Drosophila melanogaster*. Several other potassium channels with a high-sequence homology are identified in vertebrates followed and form now together with the K_V1 family [28]. At least six genes ($K_V1.1$–$K_V1.6$) with different physiological functions belong to this family.

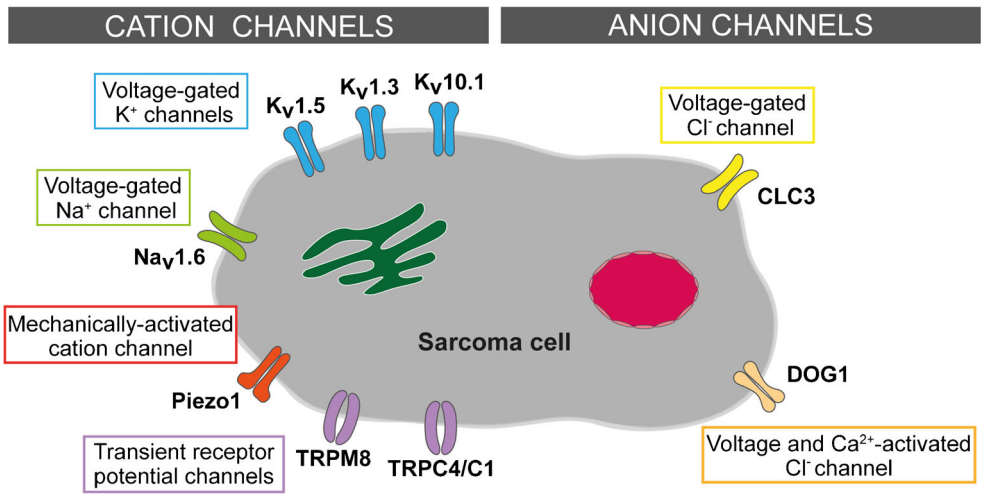

Fig. 2 Involvement of different types of ion channels in sarcoma

Table 1 Dysregulated expression of ion channels in sarcoma. List of in this review described ion channels involved in sarcoma tissue and cell lines. Human names of proteins and genes are shown

Ion channel protein name	Gene name	Patient sarcoma tissue	Sarcoma cell line	Reference
K_V10.1	KCNH1	Rhabdomyosarcoma, liposarcoma, osteosarcoma	Fibrosarcoma, rhabdomyosarcoma, liposarcoma, osteosarcoma	[42, 68–71]
K_V1.3	KCNA3	Leiomyosarcoma, alveolar rhabdomyosarcoma, embryonal rhabdomyosarcoma	Osteosarcoma	[7, 8, 72]
K_V1.5	KCNA5	Leiomyosarcoma, alveolar rhabdomyosarcoma, embryonal rhabdomyosarcoma, Ewing sarcoma	Osteosarcoma, Ewing sarcoma	[7, 8, 55, 66]
Na_V1.6	SCN8A	Ewing sarcoma		[33]
CLC3	CLCN3		Osteosarcoma	[19]
DOG1, Anoctamin-1	DOG1, ANO1, TMEM16A	Gastrointestinal stroma tumor	Gastrointestinal stroma tumor	[6, 65]
TRPM8	TRPM8	Osteosarcoma		[63, 73]
TRPC4/C1	TRPC4/TRPC1		Synovial sarcoma	[43]
Piezo1	PIEZO1		Osteosarcoma, synovial sarcoma	[38, 57]

A typical member of the family consists of a pore-forming α-unit spanning the membrane six times. Four α-subunits (homo- or heterotetrameric) form a K_V channel. The channel may also contain auxiliary cytoplasmic β-subunits. These β-subunits have an influence on biophysical properties, regulation, and/or localization of the channel [3, 28, 61]. The first four transmembrane segments (S1–S4) of the α-subunit constitute the voltage sensor, and the last two segments (S5–S6) flank a pore-forming loop. The channels contain a highly conserved structural element known as the selectivity filter, which allows K^+ ions to pass at nearly their diffusion limit, while practically blocking other ions out [41]. A conserved motif near the C-terminus connects all members of the K_V1 family. Variations of this motif between the members account for their different cell surface expression and localization [28, 39]. K_V channels play a crucial role in a plethora of cellular processes, e.g., the functioning of excitable cells, regulation of apoptosis, cell growth, and differentiation [29].

Ether a go-go (Eag = K_V10.1) potassium channel

A number of ion channels are already known to be associated with tumors. K_V10.1 is now the first ion channel directly related to tumor progression [47]. The K_V10.1 channel was first cloned from a *D. melanogaster* mutant exhibiting leg-shaking behavior under ether anesthesia [64]. Under physiological conditions, the expression of K_V10.1 (KCNH1) is restricted to the adult brain and few peripheral cell populations and is not expressed in the connective tissue [42]. The first evidence for an oncogenic potential of the K^+ channel was described by Pardo et al. already in 1999 [48]. K_V10.1 is involved in the cell cycle progression of tumor cells, and K_V10.1 inhibition by antisense oligonucleotides significantly reduces cell proliferation in tumors.

K_V10.1 is strongly overexpressed in various tumor types. K_V10.1 channel activity in the human tumor was shown for the first time in primary cultures from cervical cancer using whole-cell patch-clamp recordings [20]. In a study with 210 soft tissue sarcoma patients, Mello de Queiroz et al. showed that K_V10.1 is aberrantly expressed in over 70 % of sarcomas by immunohistochemistry [42]. The frequency of K_V10.1 expression depends on the histological type: Rhabdomyosarcoma and liposarcoma revealed frequencies of 82 % or 56 %, respectively. However, the expression of K_V10.1 neither correlates with epidemiological nor with pathological parameters like tumor size or grade. By analyzing the clinical course and outcome of liposarcoma patients, they correlated a high level of K_V10.1 expression with a bad prognosis and aggressiveness of the tumor.

In another study by Wu et al., samples of 109 liposarcoma patients were examined [71]. They also found K_V10.1 aberrantly expressed in over 67 % of the cases but showing no correlation of K_V10.1 expression with clinicopathological features of liposarcoma. In both studies, inhibition experiments by using RNA interference in established sarcoma cell lines (fibrosarcoma, rhabdomyosarcoma, and liposarcoma) resulted in a decrease of cell proliferation and colony-forming, underlining the importance of K_V10.1 for tumor survival and pointing forwards a possible role of K_V10.1 as a biomarker in liposarcoma [42, 71].

Wu et al. also investigated the involvement of K_V10.1 expression in osteosarcoma [68]. In 71.4 % of 42 examined osteosarcoma patients, K_V10.1 was overexpressed. Again, the expression could not be correlated with any epidemiological parameter. In order to evaluate the potential of K_V10.1 as a therapeutic target in osteosarcoma, a short hairpin RNA (shRNA) targeting K_V10.1 was designed. The shRNA was applied to the human osteosarcoma cell line MG-63, as well as to mice of a xenograft osteosarcoma model. The application

led to a decrease in angiogenesis and tumor growth. Wu et al. propose a suppression of tumor growth via the vascular endothelial growth factor—phosphoinositide 3-kinase—protein kinase B signaling pathway [69]. A combination of K_V10.1 suppression and simultaneous tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) overexpression in MG-63 and the xenograft osteosarcoma mouse model led to synergistic anti-tumor effects [70]. In summary, these results highlight the role of K_V10.1 in tumor proliferation, growth, and angiogenesis.

Promising treatment options targeting K_V10.1 that have been described to reduce tumor progression/metastasis in the last years include monoclonal antibodies, antisense oligonucleotides/siRNA, pharmacological K_V10.1 channel blockers like astemizole, or imipramine [18, 24, 27, 31, 45].

K_V1.3 and K_V1.5 potassium channels

Especially two members of the K_V1 family, K_V1.3 and K_V1.5, have been connected with the development and progression of cancer. In contrast to K_V10.1, K_V channels are widely expressed in the body. Pathological states in which these channels are involved can be attributed to a changed quantity of the channels [9, 16].

K_V1.3, also known as KCNA3, is an intronless gene coding for a K^+ channel expressed in a variety of different cell types and tissues, including microglia, osteoclasts, vascular smooth muscle cells, and leucocytes of the immune system. The channel belongs to the delayed rectifier class that allows nerve cells to effectively repolarize after an action potential [28, 72]. The channel is activated very fast and shows C-type-dependent inhibition and recovery. The modulation of K_V1.3 is an important mechanism for apoptosis. In the past years, K_V1.3 has been implicated with proliferation and growth of several different cancer types, e.g., breast and prostate cancer and gliomas. In rat prostate cell lines, K_V1.3 currents have been detected by electrophysiological patch-clamp recordings [22]. However, the mechanism underlying the involvement of K_V1.3 in tumorigenesis is under debate [9, 39].

KCNA5 codes for member 5 of the K_V1 voltage-gated potassium channel family (K_V1.5). K_V1.5 is expressed in various tissues like the heart, the brain, and skeletal muscles. In humans, the channels underlie the cardiac ultra-rapidly, activating delayed rectifier K^+ current, and has a crucial role in cell cycle regulation. The channel is regulated by extracellular potassium and pH [28, 36, 66].

K_V1.3 and K_V1.5 are co-expressed in several tissues like brain and muscle and are remodeled during tumorigenesis [9]. In 2013, Wu et al. investigated the expression of K_V1.3 in osteosarcoma cells [72]. They have shown that K_V1.3 is upregulated in MG-63 osteosarcoma cells. The application of a K_V1.3 specific inhibitory shRNA significantly reduced cell proliferation and induced apoptosis in the sarcoma cells. Furthermore, the inhibition of K_V1.3 in MG-63 xenografts on nude mice suppressed the growth of tumors. Shortly after these findings, the relevance of K_V1.5 expression in osteosarcoma was studied [66]. K_V1.5 was aberrantly expressed in osteosarcoma cells. K_V1.5 specific inhibition via shRNA significantly suppressed the proliferation of MG-63 osteosarcoma cells and arrested the cells in the G_0/G_1 phase of the cell cycle. Hence, targeting the ion channels K_V1.3 or K_V1.5 may be a novel therapeutic strategy for the treatment of osteosarcoma.

In a study by Bielinska et al., leiomyoma and leiomyosarcoma samples of patients were studied for K_V1.3 and K_V1.5 expression [8]. K_V1.3 and K_V1.5 are remodeled in human smooth muscle sarcoma. The expression of K_V1.3 was strongly enhanced in leiomyosarcomas compared to leiomyomas or healthy tissue, and also the expression of K_V1.5 was elevated in both tumor types. The high expression levels could be correlated with malignancy and aggressiveness of the sarcoma. The same group also investigated K_V1.3 and K_V1.5 expression in skeletal muscle sarcoma [7]: Aggressive alveolar rhabdomyosarcoma (ARMS) and embryonal rhabdomyosarcoma (ERMS) were studied. The results of the study revealed that K_V1.5 expression was moderate in adult muscle and low in ERMS, whereas it was notable in ARMS and embryonic samples. Interestingly, K_V1.3 expression showed no major differences between ARMS/ERMS and healthy samples. The authors state a correlation of K_V1.3 and K_V1.5 expression with tumor malignancy. These findings indicate that K_V1.3 and K_V1.5 represent potential targets for the treatment of human leiomyosarcoma and rhabdomyosarcoma. An in silico analysis of the miRNA expression in leiomyosarcoma compared to smooth muscle samples revealed a differential expression of various miRNAs involved in molecular pathways in sarcoma samples [5]. These miRNAs represent a possible target for leiomyosarcoma therapies.

In contrast to the aforementioned studies showing elevated expression of K_V1.3 and K_V1.5 channels involved in tumor progression, a study on Ewing sarcoma postulates reduced K_V1.5 expression in favor of tumor progression [55]. Ewing sarcoma is an aggressive bone or soft tissue tumor characterized by overexpression of polycomb proteins, which methylate (i.e., silence) target genes involved in cell differentiation. It was shown that in particular KCNA5, the gene of K_V1.5 was epigenetically repressed contributing to cancer cell survival and proliferation (Fig. 1). Together with the aforementioned shRNAs, natural molecules like scorpion toxins could act as K_V1.3 channel blockers for therapeutic applications [46].

Voltage-gated Na^+ channel Na_V1.6

Voltage-gated sodium channels (Na_V) comprise a family of ten members that are widely distributed in neurons of the central nervous system [4, 15, 23] and may play a role in cancer [49].

The Na^+ selective channels efficiently propagate action potentials when the membrane potential is depolarized by an influx of Na^+ ions. The structure of Na_V channels is quite similar to the previously described K_V channels. However, compared to them, the overall similarity of Na_V channels is rather high. The monomers are composed of four homologous α-subunits, each spanning the plasma membrane six times, and auxiliary β-subunits. The composition of β-subunits depends on the localization of the channel [14, 15]. $Na_V1.6$ is encoded by the SCN8A gene and can be found in high density in nodes of Ranvier. The unique properties of the channel allow it to sustain repetitive excitation [15]. A recent study by Hernandez-Muñoz et al. investigated the expression of the transcriptional repressor RING1B and the subsequent influence on $Na_V1.6$ in 16 primary Ewing sarcoma specimens [33]. RING1B was shown to inhibit the promotor of SCN8A. It is highly expressed in Ewing sarcomas leading to suppressed $Na_v1.6$ expression. The authors postulate that a reduced function of $Na_V1.6$ protects the Ewing sarcoma cells from apoptosis and the signaling pathway most likely impaired is NF-κB.

Voltage and Ca^{2+}-activated Cl^- channel DOG1 (TMEM16A, Anoctamin1)

Voltage- and calcium-activated chloride channels (CaCCs) play an essential role in cell physiology and are expressed in many different cell types. The channels are involved in the regulation of neuronal and cardiac excitability, regulation of vascular tone, smooth muscle contraction, and transepithelial Cl^- secretion [32]. The CaCCs are hard to classify due to missing drugs that could block one specific channel and the difficulty to determine the molecular identity. The TMEM16A (transmembrane member 16A) protein was identified as a member of the CaCCs [21]. The protein has eight putative transmembrane segments and intracellular N- and C-termini. The channels are assembled by dimers. TMEM16A appears in various isoforms generated via alternative splicing and the isoforms differ in voltage dependence and Ca^{2+} sensitivity [21]. In 2004, TMEM16A was also named gastrointestinal stromal tumor 1 (DOG1), as it was found to be ubiquitously expressed in gastrointestinal stroma tumors (GIST) [65]. West et al. have shown that 97.8 % of 139 scorable GIST samples of patients were positive for DOG1 while only 4 of 438 non-GIST cases also showed a positive immunoreaction to DOG1 [65]. DOG1 was quickly included as a biomarker, but the functional role was still unclear at that time. In 2014, electrophysiological studies from Berglund et al. in GIST882 cells revealed that the DOG1-mediated Cl^- current is voltage and Ca^{2+} activated and regulated by DOG1 channel activators and inhibitors [6]. This group also reported a high expression of DOG1 in GIST cells and that the cellular localization of DOG1 varies between imatinib-sensitive and resistant GIST cells. However, in vitro experiments with DOG1-regulating modulators revealed only a small effect of DOG1 on cell viability and proliferation of GIST cells. The reason for this high and rather specific expression of DOG1 in GIST remains unclear and further investigations are needed to shed light on the function of DOG1 and its potential as a therapeutic target.

Voltage-gated chloride channel 3 (CLC-3)

Voltage-gated chloride channels (CLCs) constitute an evolutionarily well-conserved superfamily, which includes two distinct functional groups: voltage-gated chloride channels and Cl^-/H^+ antiporters. Their functions in higher animals include cell volume regulation, signal transduction, transepithelial transport, control of electric excitability, and acidification of intracellular organelles [37]. Nine CLC-like proteins have been cloned from mammals. CLC-3 is one member of the CLC family and participates in the process of proliferation, apoptosis, and drug resistance in many types of cancers [35]. The expression of CLC-3 produces outwardly rectifying Cl^- currents that can be inhibited by the activation of protein kinase C [35]. In a study from Du et al., it was shown that CLC-3 is upregulated in human osteosarcoma cells and in cells with high metastatic potency [19]. The expression of CLC-3 correlated with the rate of cell proliferation. A siRNA-induced inhibition of CLC-3 arrested the sarcoma cells in phase G_0/G_1 of the cell cycle. Additionally, the activation of Akt-GSK-3β via phosphorylation was suppressed. These findings indicate that CLC-3 may be a potential target for osteosarcoma therapy.

Transient receptor potential (TRP) channels

The TRP superfamily of cation channels can be divided into seven subfamilies: five group 1 subfamilies (TRPA (ankyrin), TRPC (canonical), TRPM (melastatin or long TRPs), TRPN (Nomp-C homologues), and TRPV (vanilloid)) and two group 2 subfamilies (TRPML (mucolipin) and TRPP (polycystin)). Members of the TRP channel family share the feature of six transmembrane domains (S1–S6) and intracellular N- and C-termini containing putative protein interaction and regulatory motifs [25]. Comparable with voltage-gated K^+ channels, tetramers form cation-selective pores. However, TRP channels are rather classified according to their amino acid sequence than to their cation selectivity. TRP channels play a critical role in sensory physiology and have also importance for motile function [26, 62]. Various TRP channels have been associated with cancer [39, 54], but their involvement in sarcoma is still not clear.

TRPM8

The mammalian TRPM family has eight members. The transient receptor potential melastatin 8 (TRPM8) channel, also

known as "cold receptor" was originally identified in prostate tissue [60]. This early study already showed that TRPM8 expression is elevated in prostate cancer cell lines and several other cancer cell line. Soon after the identification of the channel, it was shown that TRPM8 acts as ion channel being activated by cold temperature and the cooling agent menthol in peripheral sensory neurons, and therefore, plays a critical role in the detection of cold temperatures [50]. TRPM8 constitutes a nonselective cation channel with a modest Ca^{2+} permeability [1]. TRPM8-mediated currents characterized by a high Ca^{2+} selectivity have been reported to be induced by stimulation of prostate cancer cells by either coolness, menthol, or icilin [59].

The group of Wang et al. was the first to demonstrate that TRPM8 is highly overexpressed in osteosarcoma by investigating 10 samples from osteosarcoma patients [63]. A siRNA-induced knockdown of TRPM8 in osteosarcoma cell lines induced an impaired intracellular Ca^{2+} homeostasis. Furthermore, the inhibition of TRPM8 enhanced the efficacy of epirubicin-induced apoptosis in the sarcoma cells. The authors propose that TRPM8 is required for cell proliferation and motility. They show that the suppression of TRPM8 blocks the Akt-GSK-3β pathway and the subsequent phosphorylation of p44/p42 and FAK. These results reveal that TRPM8 may play a role as a therapeutic target in osteosarcoma.

A subsequent clinical study with primary osteosarcoma patients by Zhao and Xu involving two consecutive cohorts of patients aimed to investigate the expression and prognostic significance of TRPM8 in osteosarcoma [73]. The two cohorts A and B contained 20 and 98 patients, respectively. They confirmed the previous findings of a significantly higher expression of TRPM8 compared to normal bone tissue [63, 73]. Samples of cohort A were examined by qPCR and samples of cohort B by immunohistochemistry for expression of TRPM8. Osteosarcoma patients compared to the healthy control group showed a significantly higher expression of TRPM8 (3.34 ± 0.23 vs. 0.55 ± 0.12; $P < 0.05$) and 60.2 % positivity for TRPM8, respectively. TRPM8 levels were markedly higher in patients with metastasis or osteosarcoma at higher clinical stage compared to those with a lower clinical stage and no metastasis. Therefore, a higher TRPM8 expression is associated with an unfavorable prognosis for the patients [73]. Thus, TRPM8 may serve as a clinical biomarker in the diagnosis or prediction of clinical outcome in patients with osteosarcoma.

Heteromeric TRPC4/C1

For the mammalian TRPC family, seven members have been described. However, in humans, only six are expressed as the human TRPC2 is a pseudogene. The mammalian TRPC family can be divided into 4 subsets according to functional similarities and sequence homology: TRPC1, TRPC2, TRPC3/6/7, and TRPC4/5 [62]. TRPCs, in general, are nonselective Ca^{2+} permeable cation channels that need phospholipase C for their activation [51]. TRPC1 can form heterotetramers with TRPC4 and TRPC5 [44].

In human synovial sarcoma cells (SW982), the heterotetramer TRPC4/C1 is expressed. Muraki et al. investigated the cytotoxic effect of the organic compound Englerin A on human synovial sarcoma cells [43]. There, they identified a sarcoma selective cytotoxicity of Englerin A, but not in normal cells. It is proposed that TRPC4/C1 is the primary target of Englerin A and the effect is mediated by Na^+ loading via activation of heteromeric TRPC4/C1 channels coupled with insufficient Na^+/K^+-ATPase activity. These findings also indirectly indicate an aberrant expression of TRPC4/C1 in synovial sarcoma cells, as normal cells are not affected.

Mechanically activated cation channel Piezo1

In 2010, Piezo1 was affirmed to be a mechanically activated cation channel [17]. Piezo1 constitutes a huge membrane protein with 14 transmembrane segments. The trimeric complex has the shape of a propeller with three curved "blades" encircling a central poor permeable for cations. The channel is mainly expressed in tissues exposed to fluid pressure and flow. Piezo1 can be activated by mechanical stress, shear stimuli on the cell membrane, and by chemical agonists, e.g., 2-[5-[[(2,6-dichlorophenyl)methyl]thio]-1,3,4-thiadiazol-2-yl]-pyrazine (Yoda1) [67].

A recent study provided evidence for the involvement of Piezo1 in osteosarcoma [38]. They have shown that Piezo1 protein is expressed in human osteosarcoma cells (MG63 and U2). In a mechanical stretch model with human osteosarcoma cells, it was shown that Piezo1 promoted apoptosis of osteosarcoma cells under stretch force, which could be suppressed via shRNA inhibition of Piezo1. However, in in vivo experiments with nude mice, an inhibition of Piezo1 could significantly restrain tumor growth after 4 weeks [38]. In 2018, Suzuki et al. investigated the possible role of Piezo1 in cell viability of synovial sarcoma cells [57]. They showed that Piezo1 is highly expressed in synovial sarcoma cells SW982 and could be activated by the Piezo1 agonist Yoda1 in a concentration-dependent manner. A siRNA-induced Piezo1 knockdown significantly induced reduced cell viability in sarcoma cells. However, the molecular mechanism explaining Piezo1 involvement in cell viability is yet to be elucidated. In conclusion, these described publications indicate that Piezo1 may be a novel potential therapeutic target for the treatment of osteosarcoma/synovial sarcoma.

Concluding remarks

Sarcomas show a plethora of more than 100 different malignant tumors, some of which differ greatly in terms of their

biological behavior, their prognosis, and their response to different therapeutic approaches. The variety of different sarcoma types together with the diversity of available drugs and the requirement of an exact knowledge of the various side effects demands a high degree of specialization and experience and makes sarcoma treatment very difficult. A safe and rapid diagnosis and the identification of the type of sarcoma are fundamental for successful treatment. Therefore, there is a high need for new strategies and approaches to face the difficulties of sarcoma tumor treatment and diagnosis. A specified pattern of ion channel expression could support a safe and fast sarcoma therapy. Because of their large functional and structural diversity, K^+ channels have enormous potential as targets for cancer treatment.

Inhibition of ion channels by pharmacological tools, monoclonal antibodies, or antisense oligonucleotides/siRNA may be an attractive strategy to counteract sarcoma growth, prevent metastasis, and enhance apoptosis of sarcoma cells. Further studies are required to validate these ion channels as a potential diagnostic target for the treatment of the various sarcoma types and to possibly identify new, patient-tailored, therapeutic approaches.

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