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Mechanosensitive ion channels push cancer progression

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ABSTRACT

In many cases, the mechanical properties of a tumor are different from those of the host tissue. Mechanical cues regulate cancer development by affecting both tumor cells and their microenvironment, by altering cell migration, proliferation, extracellular matrix remodeling and metastatic spread. Cancer cells sense mechanical stimuli such as tissue stiffness, shear stress, tissue pressure of the extracellular space (outside-in mechanosensation). These mechanical cues are transduced into a cellular response (e. g. cell migration and proliferation; inside-in mechanotransduction) or to a response affecting the microenvironment (e. g. inducing a fibrosis or building up growth-induced pressure; inside-out mechanotransduction). These processes heavily rely on mechanosensitive membrane proteins, prominently ion channels. Mechanosensitive ion channels are involved in the Ca^{2+}-signaling of the tumor and stroma cells, both directly, by mediating Ca^{2+} influx (e. g. Piezo and TRP channels), or indirectly, by maintaining the electrochemical gradient necessary for Ca^{2+} influx (e. g. K_{2P}, K_{Ca} channels). This review aims to discuss the diverse roles of mechanosenstive ion channels in cancer progression, especially those involved in Ca^{2+}-signaling, by pinpointing their functional relevance in tumor pathophysiology.

1. Introduction

In many cases the mechanical properties of a tumor are different from those of the host tissue [1]. This has always been the basis for the clinical detection of a tumor (e. g. breast or prostate cancer) by palpation. This can nowadays be complemented by modern imaging techniques such as MRI [2] or ultrasound elastography [3]. The stiffness of the tumor stroma [4] and the tissue pressure (e. g [5].) are usually higher than those of the normal organs.

Increased intratumor pressure can have intrinsic and extrinsic origins. Intrinsically developed intratumor pressure is either generated by the direct pressure of the growing tumor on itself and its surroundings (growth-induced pressure); by the fibrotic, desmoplastic extracellular matrix compressing the tumor; by the lack of functional lymphatic vessels; or by aberrant, leaky capillaries permeable to osmotically active colloidal substances [6]. These factors together lead to an increase in both hydrostatic and oncotic pressures, thereby increasing the interstitial fluid pressure. On the other hand, extrinsic tumor pressure is generated by increased intracavitary pressure due to secondary effects of the tumor - e. g. ascites or brain edema. In some tumors, such as breast cancer and pancreatic ductal adenocarcinoma (PDAC), matrix production becomes particularly excessive, forming a so-called desmoplastic reaction in the proximity of the tumor [7,8]. Synergistically, these forms of pressure act by an increased intratumor pressure – in case of PDAC it can increase from ˜8 mmHg in the healthy tissue to as high as 130 mmHg in the tumor [9].

From a clinical point of view it is of note that tumor stiffening correlates with its aggressiveness [10]. Thus, the characteristic mechanical properties of a tumor are not only epiphenomena of tumor growth, but they are also important regulators of tumor progression by affecting the behavior of both tumor and stromal cells as illustrated by the following examples. Breast cancer cells respond to the mechanical cues they receive from the extracellular matrix [11]. Pancreatic stellate cells (PSCs) which are responsible for the excessive production of extracellular matrix proteins in PDAC, are activated by an elevated pressure and substrate rigidity [4,12]. Tumor and stroma cell migration itself, which is essential for metastasis, also generates mechanical signals within the cells that modulate the migratory behavior [13]. Finally, also the organs in which cancer originates and the sites of metastases may impose great mechanical challenges upon cancer cells. Remarkable examples include cancer types that metastasize to both soft tissue (e.g. brain) and hard tissue (e.g. bone) such as breast and lung cancer [14].

The fact that cancer and tumor stroma cells are able to respond to diverse mechanical stimuli from their environment implies their ability to sense these cues (Fig. 1). There are many potential mechanisms of mechanosensation and we refer to some excellent recent reviews [15,16]. Examples of prominent molecular players in this context

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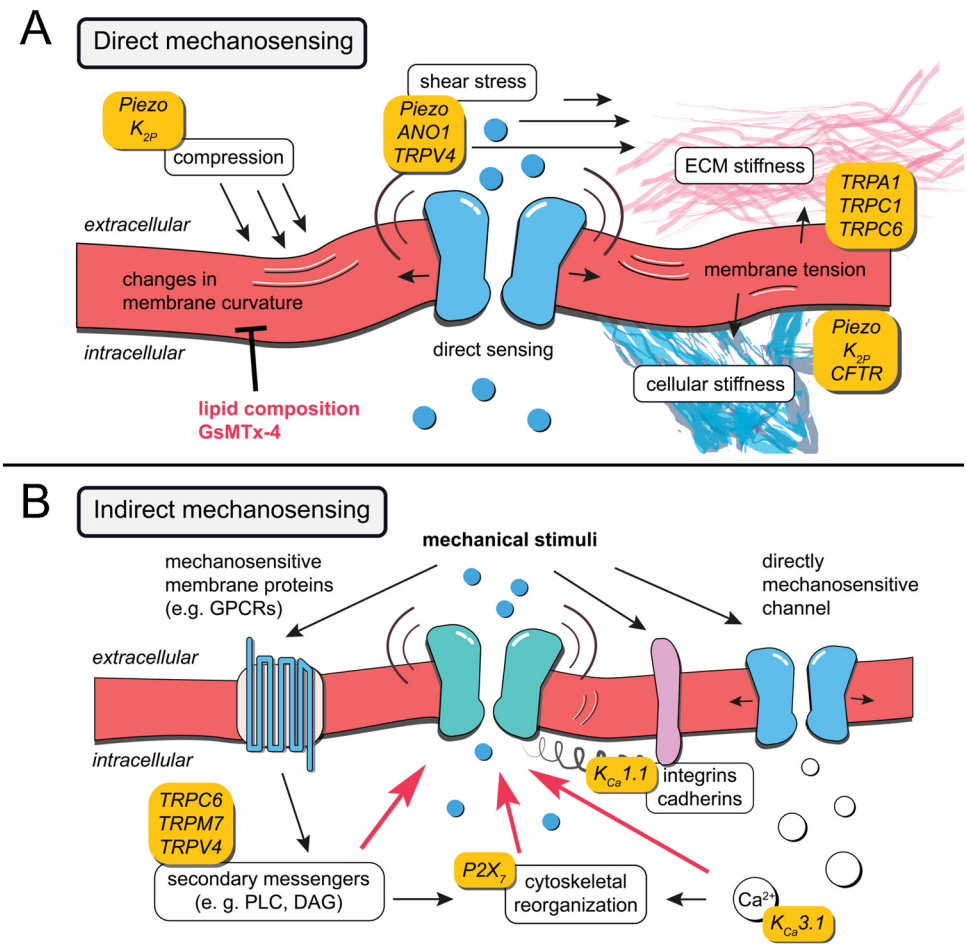

Fig. 1. Mechanosensitive channels can be gated either directly by a physical force or downstream signaling cascades. Direct mechanosensing **(A)** is caused mainly by the physical changes of the plasma membrane. In tumor tissue, compression leads to changes in cell membrane curvature what causes channels like Piezo and K_{2P} to open. Molecules which distort membrane physical properties (e. g. GsMTX-4) therefore inhibit mechanosensitive channels. Since tumor environment is often associated with fibrosis and increased extracellular matrix stiffness, membrane tension may also be augmented. Piezo, K_{2P}, CFTR and several TRP channels present on plasma membrane can sense these signals and through ion fluxes, mediate tumor cell responses. In case of ductal cells and cells of the vascular lining, shear stress is another important trigger for mechanosensitive channels. Channels, such as Piezo, ANO1, TRPV4 represent shear stress sensors which mediate ion fluxes in healthy and tumor-associated cells. Indirect mechanosensing **(B)** is a multi-step process that can be mediated through various pathways. Mechanical stimuli affect several mechanosensitive proteins on the plasma membrane and subsequent activation of intracellular cascades eventually lead to opening of (indirectly) mechanosensitive channel. For instance, stimulation of G-protein coupled receptors (GPCRs) evokes production of secondary messengers which in turn activate several TRP channels. Cytoskeletal reorganization and integrin/cadherin signaling may also cause channel opening, as observable in case of $P2X_7$ and $K_{Ca}1.1$, respectively.

include integrins, focal adhesion complexes, transcription factors such as YAP/TAZ as well as G-protein coupled receptors and mechanosensitive ion channels [17,18].

The purpose of the present review is to discuss the role of mechanosensitive ion channels in cancer progression (Fig. 2). We will focus in particular on Ca^{2+} signaling that depends on these channels and investigate in detail the roles of Piezo1, Piezo2 and selected members of the TRP channel family (TRPC1 & 6, TRPV4, TRPA1 and TRPM7). In addition, we will also touch upon mechanosensitive K^+ channels from the K_{2P} family and on Ca^{2+}-sensitive K^+ channels which are effectors of the Ca^{2+} signals elicited by Ca^{2+}-permeable mechanosensitive channels.

2. Cross-talk between Ca^{2+} permeable mechanosensitive channels and mechano- or Ca^{2+}-sensitive K^+ channels

Piezo channels and mechanosensitive TRP channels are Ca^{2+}-permeable, non-selective cation channels. As for any other ion channel, cation/Ca^{2+} influx is largely driven by the membrane potential. On the other hand, mechanosensitive cation influx will elicit a membrane depolarization and thereby limit its magnitude. To overcome this limitation, cells can express Ca^{2+}-activated K^+ channels (K_{Ca}) to maintain the electrical driving force for Ca^{2+} influx. For example, such functional coupling has been found in endothelial cells between TRPV4 and $K_{Ca}3.1$ channels, where the hyperpolarization due to the function of $K_{Ca}3.1$ channels eventually leads to Ca^{2+} overload and vascular leakage. This response is absent in endothelial cells from $K_{Ca}3.1^{-/-}$ mice [19]. Similarly, TRPV4 and $K_{Ca}2$ channels cooperate during osmosensing of paraventricular neurons. Following TRPV4-mediated Ca^{2+} influx, activation of $K_{Ca}2$ channels causes a hyperpolarization and reduces the electrical activity of these neurons [20]. In Piezo1-expressing neuroblastoma cells the response to mechanical stimulation, i.e firing of action potentials because of Piezo1-induced depolarization, is blunted by the simultaneous expression of the mechanosensitive $K_{2P}4.1$ channel (TRAAK) [21].

These examples clearly show that the cellular responses to mechanical stimulation not only depend on the presence or absence of mechanosensitive channels. It is equally important which type(s) of mechanosensitve channels are expressed – only either K^+ channels or nonselective cation mechanosensitive channels, a combination of both, or a combination of cation nonselective mechanosensitive channels and K_{Ca} channels. In addition to its impact on mechanosensitive Ca^{2+} influx, the membrane potential is also crucial for the function of the Na^+/Ca^{2+} exchanger. At hyperpolarized membrane potentials it is usually operating in the forward mode mediating Ca^{2+} export. The transport direction may change so that it is operating in the reverse mode at depolarized membrane potentials and contributing to Ca^{2+} loading [22]. In the cancer field, the intricate functional interdependence of multiple classes of (mechanosensitive) ion channels and transporters is only in the beginning to be investigated. This is of high relevance, because of the outlined mechanical impact on cancer progression (Fig. 2).

3. Biophysical aspects of mechanosensitive gating

Mechanosensitive ion channels respond with channel gating to sensing changes of physical stress of their microenvironment. Here, we only give a brief introduction into the biophysical aspects of mechanosensitive channels. For more thorough reviews, see [23,24]. Essential requirements for sensing mechanical stress are that 1. membrane stress can reach the channels and 2. the channels change shape between

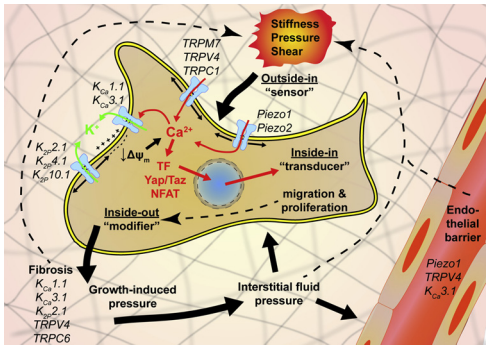

Fig. 2. The primary forms of mechanical stress affecting cancer cells and the tumor stroma are altered tissue stiffness, increased intratumor pressure and shear stress. These factors can affect the cells by an outside-in „sensor" mechanism, in which the cells sense mechanical cues through mechanosensitive ion channels. These channels can be either permeable to Ca^{2+} (TRP and Piezo) and thereby directly lead to an increase in $[Ca^{2+}]_i$. Alternatively, K^+ channels (K_{2P} and K_{Ca}) can also be mechanosensitive. Through K^+ efflux they induce hyperpolarization of the membrane potential ($\downarrow\Delta\psi_m$) that provides additional driving force for further Ca^{2+} influx. The Ca^{2+} signal activates multiple pathways and transcription factors, such as the YAP/TAZ and NFAT, that conduct the mechanical stimuli to the nucleus and initiate gene transcription. This leads to changes in cellular physiology (inside-in" transducer" mechanism) in which the cells undergo for example cell migration or proliferation in response to the mechanical cues. The altered proliferation leads to the crowding of the cells, which directly compresses the microenvironment and other cells, leading to growth-induced pressure; moreover, cancer cells alter their surroundings by initiating stromal fibrosis (inside out "modifier" mechanism). In a fibrotic tumor, increased matrix stiffness stimulate mechanosensitive channels which can further activate stroma and/or cancer cells. These activated tumor stroma cells secrete more matrix proteins further increasing the amount of fibrotic tissue. Through these mechanisms, blood vessels become also compressed in the tumor, and through the compromised endothelial barrier, more osmolytes enter the tumor tissue, increasing the net interstitial fluid pressure. As a result of the mechanisms detailed above, the net intratumor pressure gradually increases which leads to a positive feedback cycle on the tumor and stromal cells.

closed and open states. The stress signals to open mechanosensitive channels directly can arise from a multitude of stimuli, as demonstrated by Fig. 1A: shear, especially in the blood vessels, compression, lipid bilayer tension, local changes in membrane curvature and composition (e.g. lipid rafts) [25]. Mechanosensitive K_{2P} channels are blocked by lipids which get access to ion conduction through openings in the channel protein to the surrounding membrane. Mechanical stress relieves this inhibition because of conformational changes of the channel protein [24].

Alternatively, channel gating can be induced indirectly, as illustrated in 1B. The mechanical stimulus is detected by a mechanosensitive molecule (often G-protein coupled receptor) so that the channel is activated by an intracellular signaling cascade. Gating of mechanosensitive channels can also occur indirectly by tethers (e. g. integrins, cadherins) of the nearby scaffolding elements, such as the extracellular matrix or the actin cytoskeleton that either dampen or amplify the signal [26]. Also, mechanosensitive ion channels (namely TRPV4 and Piezo1) can be present in primary cilia, and contribute to its function as a mechanosensor [27]. Whether this plays a role in tumor progression, however, is questionable, as many malignancies are characterized by decrease or loss of primary cilia [28]. In the context of the present review it is notable that many authors employ the acute exposure of cells to a hypotonic environment as a "mechanical "stimulus. Note, that osmotic pressure is distinct from mechanical stress, as osmotic stress mainly affects the cytoskeletal components of the cell and not necessarily stretches the cell membrane [29].

The classical inhibitors of mechanosensitive ion channels include Gd^{3+} and the *Grammostola spatulata* spider toxin GsMTx-4. These compounds all act by associating with lipid bilayers [30–32], and thus dampening the effect of mechanical stress on mechanosensitive ion channels.

4. Piezo channels in cancer

The mechanosensitive, cation-selective Piezo channels, namely Piezo1 and Piezo2, are ubiquitously expressed in the human body [33]. They are involved in mechanosensing as well as mechanotransduction *in vitro* and *in vivo* [34,35]. Piezo channels are known to sense mechanical perturbations in the membrane bilayer (Fig 1A) [36]. Direct mechanotransduction is achieved via flexible amino acid side chains in their numerous transmembrane domains which form the "propeller blades" of the channel trimer [37]. Moreover, Piezo1 deforms the cell membrane locally into a dome which is ~18 nm wide and ~6 nm deep. This makes that particular site even more susceptible to mechanical stretch [38]. Also, Piezo1 is present in primary cilia, but whether it affects ciliary Ca^{2+} influx due to fluid shear could not be verified yet [27]. For a more detailed overview on the mechanosensory function of Piezo channels, see [39].

The unique features of the Piezo channels combined with their ubiquitous expression raised the question whether Piezo expression and function is altered in cancer. The channels were mainly investigated in cancer types originating from tissues prone to a high degree of mechanical stress. In detail, increased expression of Piezo1 in the cell membrane was described in breast cancer [40], gastric cancer [41], bladder carcinoma [42], osteosarcoma [43] and synovial sarcoma [44]. In mouse bladder carcinoma cells Piezo1 is highly expressed in the cell membrane as revealed by immunohistochemistry. However, it is not clear, whether the channel is involved in cancer progression [42]. In the MCF-7 cell line, Piezo1 is involved in 2D cell migration [40], and in gastric cancer cell lines pharmacological inhibition or knockdown of Piezo1 impairs 2D migration and 3D invasion, as well as arresting the cells in G_0/G_1 phase of the cell cycle inhibiting cell proliferation [41,45]. Also, Piezo1 is highly upregulated in thyroid cancers caused by the Chernobyl accident in response to iodine-131 [46].

On the other hand, loss of Piezo1 function may play a role in lung cancer. On mRNA level, Piezo1 is down-regulated in both small-cell lung carcinoma (SCLC) and non-small-cell lung cancer (NSCLC) [47]. In NSCLC knockdown of Piezo1 and Piezo2 by shRNA promotes *in vitro* cell migration and *in vivo* tumor growth [48]. Also in SCLC cell lines, reducing expression of Piezo1 using siRNA induces anchorage-independence in cancer cells and facilitates 2D and 3D migration [49].

Piezo2 overexpression was only detailed in case of bladder carcinoma, where it is upregulated in high-grade tumors [42]. In addition to regulating cancer cell behavior, Piezo2 may also be involved in tumor angiogenesis [50]. The reason why cancer cells favor Piezo1 to Piezo2 is to date unknown. A possible explanation could be that Piezo1 transduces a very broad frequency range of repetitive mechanical stimuli possibly occurring in carcinogenesis. In contrast, Piezo2 is most effective at very low frequencies [51].

Whether Piezo1 has implications in fibrosis and the desmoplastic reaction in various forms of cancer is still unclear. It is known that Piezo1 mediates pressure-mediated pancreatitis [52], and therefore, it is possible that the channel also contributes to a chronic pancreatitis which may be a precursor lesion of PDAC.

Whether Piezo1 inhibition could be therapeutically beneficial in cancer is a complicated question that still needs to be investigated. The first hurdle to overcome is that there is no specific inhibitor of Piezo1 available yet, as only non-specific inhibitors are known such as Gd^{3+}, ruthenium red and the GsMTx-4 [33]. This may change soon as the cryo-EM structure of the channel has recently been published [38,53,54]. The second major obstacle with inhibiting Piezo1 is its ubiquitous expression in the body, thus its multitude of physiological roles. A complete knockout of Piezo1 - as well as of Piezo2 - in mice results in a lethal phenotype *in utero* as the vascular development

becomes severely impaired [55–57]. Also, in adults, Piezo1 is crucial in maintaining cardiovascular homeostasis by affecting both vascular smooth muscle and vascular endothelial cells [58–60]. This may indicate the risk of significant cardiovascular side effects in case of universal inhibition of Piezo channels in the body.

5. Mechanosensitive TRP channels in cancer

Transient receptor potential (TRP) channels act as 'cellular sensors' and mediate varied stimuli (reviewed in [61]). There are six different mammalian TRP subfamilies based on their homology: TRPA (ankyrin), TRPC (canonical), TRPM (melastatin), TRPML (mucolipin), TRPP (polycystin) and TRPV (vanilloid). They are predominantly non-selective, permeable for mono- and divalent ions. Since most TRP channels are Ca^{2+}-permeable, they are crucial for calcium signaling, which is often altered in transformed tumor cells [62]. Ca^{2+} as a multifunctional second messenger is involved in many of the behavioral traits of cancer cells that underlie their aggressiveness. Examples include cell migration, adhesion, proliferation, invasion and metastasis. It activates Ca^{2+}-dependent proteins, *i.e.* calmodulin, Ca^{2+}/calmodulin-dependent protein kinase II, calcineurin and protein kinase C and activates several transcription factors among which nuclear factor of activated T cells (NFAT) is a well-known inducer of cell proliferation [63].

Several TRP channels are said to be mechanosensitive, gated either directly by physical forces like membrane stretch, or by downstream signaling cascades [64,65]. However, in the past there was some controversy with respect to the mechanosensitivity of some of the TRP channels [66]. The function of mechanosensitive TRP channels is well described for sensory receptors where they transduce thermal and mechanical cues [34]. They are also found in cancer and stroma cells and known to contribute to tumor progression [67,68]. Some of the most relevant members of the TRP channel family will be discussed in the following. The pronounced environmental challenges tumor cells are facing during tumorigenesis, metastasis and homing, make mechanosensitive TRP channels putative modulators of tumor cell behavior and thus, potential therapeutic targets [69,70]. Up to date, there is experimental evidence suggesting the involvement of mechanosensitive TRPA1, TRPC1, TRPC6, TRPM7 and TRPV4 channels in malignancies.

TRPA1: TRPA1 channels ('wasabi receptor') contain ankyrin repeats at its N-terminus which presumably act as molecular 'springs' and contribute to TRPA1 mechanosensitivity [64]. Knock-down of TRPA1 in Lewis lung carcinoma cell line (LLC-2) results in higher proliferation but decreased adhesion and invasiveness [71]. In SCLC, TRPA1 activation increases cell survival and promotes tumor progression [72]. Recent studies also suggest that TRPA1 is overexpressed in various tumors and increases the tolerance of malignant cells to reactive oxygen species [73].

TRPC1: In breast cancer, a hypoxic environment causes increased expression of TRPC1 which in turn promotes epithelial to mesenchymal transition (EMT) [74]. Similarly, channel overexpression in invasive ductal breast carcinoma may lead to more robust EMT upon transforming growth factor β (TGFβ) stimulation [75]. TGFβ was also shown to induce pancreatic cancer cell motility and accordingly, TRPC1 knock-down abolishes this process [76]. Silencing of TRPC1 (or its cooperating channel, $K_{Ca}3.1$) in MCF-7 breast cancer cell line, inhibits cell proliferation by G_0/G_1 cycle arrest [77]. Also, in NSCLC, TRPC1 knock-down inhibits epidermal growth factor (EGF)-induced cell growth [78]. In nasopharyngeal carcinoma, TRPC1 mediates cell invasiveness and production of matrix metalloproteinase 2 and 9 (MMP2, 9) [79]. In glioblastoma and also in thyroid cancer, the channel is activated upon PDGF, VEGF or sphingosine-1-phosphate stimulation and is required for cancer cell migration and chemotaxis [80,81]. We could show that TRPC1 contributes to mechanosensation during migration in transformed epithelial cells. Knockdown of TRPC1 channels impairs the detection of mechanical cues (stretch) and leads to directionally uncontrolled protrusive lamellipodial activity [82,83]. Moreover, TRPC1 channels are part of the signaling cascade underlying the activation of pancreatic stellate cells by ambient pressure. TRPC1-mediated Ca^{2+} influx rises when stellate cells are kept at an elevated pressure, although TRPC1 mRNA expression (and that of several other mechanosensitive channels) is reduced [12].

TRPC6: Another canonical TRP channel, TRPC6, is overexpressed in glioblastoma cells under hypoxic conditions. It mediates cancer progression, angiogenesis, thus being important for tumor growth and blood supply [84]. TRPC6 overexpression is also an indicator of benign prostatic hyperplasia and malignant prostate tumors and in prostate cancer cell lines [85]. High expression of this channel correlates with worse prognosis and lower patient survival in esophageal squamous cell carcinoma [86]. In the NSCLC cell line A549, inhibition of TRPC6 lowers cell proliferation and invasion [87]. While a direct link to tumor mechanics is usually not addressed by these studies, TRPC6 may also indirectly affect tumor mechanics by its role in fibrosis. In pancreatic and hepatic stellate cells TRPC6 links hypoxia to fibrosis because it is required for the activation of the cells by hypoxia. Activated stellate cells, in turn, are responsible for excessive matrix production [88,89].

TRPV4: TRPV4 is involved in mechanotransduction in processes like volume regulation and osmosensing [90]. In tumor endothelial cells, cell mechanosensitivity is often diminished, what leads to increased migration, vascularization and growth [91]. Therefore, mechanosensitive TRPV4 channel seems to be necessary for inhibition of cancer progression. Along with this assumption, Lewis lung carcinoma cells form much more pronounced tumors, and leaky, malformed vessels when injected in $TRPV4^{-/-}$ mice compared with WT mice [91]. This is probably due to lower VE-cadherin expression in $TRPV4^{-/-}$ endothelial cells [92]. Interestingly, this function of TRPV4 channels in tumor vessels is different from that in the lung vasculature where an activation of TRPV4 channels causes a severe disruption of the vascular integrity [19]. Pharmacological activation of TRPV4 inhibits proliferation of tumor endothelial cells and tumor-associated angiogenesis [93]. In gastric cancer cells, TRPV4 promotes proliferation and invasiveness, presumably through Ca^{2+}/AKT/β-catenin axis [94]. Comparative analysis of breast cancers suggests that TRPV4 promotes metastatic processes by modulating of cell stiffness and cell extravasation rather than proliferation [95]. Tissue stiffness regulation is probably mediated by secretion of various extracellular proteins, like MMP-9 upon fibronectin stimulation [96]. In cancer, this extracellular protein production may be mediated by aberrations in AKT signaling [97,98]. In normal mouse primary epidermal keratinocytes, TRPV4 is the major sensor of tissue stiffness. It regulates the YAP/TAZ nuclear translocation in cells seeded on stiff matrix and co-localizes with mesenchymal markers in bleomycin-induced fibrosis [99]. Several other studies have also come to the conclusion that TRPV4 is an important player in fibrosis [100,101]. Because fibrosis often occurs in tumors and affects tissue rigidity, one of the functions of TRPV4 in cancer is not only to respond to mechanical cues, but rather to modify the mechanical properties of the tumor stroma. Also, TRPV4 is known to be enriched in the primary cilium, which itself is involved in mechanosensation. There, the function of TRPV4 leads to flow-induced ciliary Ca^{2+}-influx [102].

TRPM7: TRPM7 is involved in basal and EGF-induced migration of A549 cells [103]. EMT in breast cancer is mediated by phosphorylation of the transcription factor STAT3 what was shown to be TRPM7 channel-dependent [104]. High expression of TRPM7 in breast cancer patients indicates poor prognosis and channel knock-down inhibits cancer migratory abilities [105]. In estrogen receptor negative invasive ductal breast carcinoma TRPM7 plays a role in cell migration independently from Ca^{2+}, but rather through its kinase activity [106]. In MDA-MB-435 melanoma cell line, previously described as breast cancer line [107], TRPM7 expression correlates with cell migratory and invasive abilities, which is probably mediated by MAPK signaling pathway activation [108]. In ovarian cancer cells, TRPM7 not only facilitates cell migration, but also cell proliferation [109]. Also, in

human PDAC, TRPM7 expression correlates with cancer progression, presumably by mediating cell migration and invasion through Hsp90α/uPA/MMP2 axis [110,111]. Using TRPM7 RNA interference, PDAC cell invasion becomes diminished [112]. Similarly to TRPC1, TRPM7 promotes migration of nasopharyngeal carcinoma cell lines (5-8 F, 6-10B). This has been linked to the permeability of the channel to Ca^{2+} [113].

Not surprisingly, there is increasing interest in the role of mechanosensitive TRP channels in malignancies. However, except for TRPV4 channel, there is not much known about the role of the channels' mechanosensitivity itself in cancer progression. Nonetheless, the changes in the physical properties of the tumor microenvironment suggest that the gating of these channels may be altered in tumorigenesis and along the metastatic cascade.

6. Ca^{2+}-activated K^+ channels

Based on their unitary single channel conductance, K_{Ca} channels come in three subfamilies: $K_{Ca}1.1$, $K_{Ca}2.1$-3 and $K_{Ca}3.1$. In addition to their basic function of setting the cell membrane potential and thereby maintaining the electrical driving force for mechanosensitive non-selective cation channels, some of them also have a more direct link to tumor mechanobiology [114]. There are several reports pointing to a mechanosensitivity of $K_{Ca}1.1$ channels (e. g. [115]), but so far it is not known whether this has a role in cancer. That $K_{Ca}1.1$ plays a "mechanical role" in cancer is likely, because it is associated with one of the important mechanosensory cellular structures, focal adhesions [116]. It promotes prostate cancer progression by forming a complex with $\alpha_v\beta_3$ integrins [114], and it is also associated with β_1 integrin in invasive fibroblast-like synoviocytes in rheumatoid arthritis [117]. Overexpression of the $K_{Ca}1.1$ pore-forming α-subunit has been described in breast cancer, glioblastoma, colon cancer [118–120]. Moreover, both the main α-subunit and the auxiliary β_3 subunit become upregulated in invasive fibroblast-like synoviocytes [121,122].

$K_{Ca}3.1$ channels are important players in cancer and there is increasing evidence that they are also important signaling molecules in cancer stroma cells (e. g. [123]). They are not directly mechanosensitive themselves (Fig 1B). Nonetheless, there is increasing evidence that they impact on tumor mechanics and thereby indirectly regulate other mechanosensitive channels: a number of studies have shown that $K_{Ca}3.1$ channels play a crucial role in the development of fibrosis in multiple organs. Accordingly, knockdown of $K_{Ca}3.1$ channels or the pharmacological blockade using TRAM-34 or senicapoc attenuate fibrosis. Examples include idiopathic pulmonary fibrosis [124–127], hepatic [128,129], renal [130,131], cardiac [132,133], as well as conjunctival fibrosis [134,135]. A common mechanism by which $K_{Ca}3.1$ channel inhibition alleviates fibrosis is by targeting (myo-)fibroblasts. The pro-fibrotic response of TGFβ1 is attenuated by reducing transcription and/or secretion of fibrotic markers such as α-smooth muscle actin, fibronectin, collagen I and collagen IV and/or by inhibiting proliferation of fibroblasts [136]. Moreover, migration of fibroblasts is markedly inhibited when they are treated either with TRAM-34 or senicapoc [137].

The role of $K_{Ca}3.1$ channels in fibrosis is very relevant in the context of this review. First of all, fibrosis is characterized by an abundant secretion of collagens and other matrix proteins and remodeling of the extracellular matrix. Eventually, this will result in altered mechanical properties of the affected tissue which usually becomes stiffer which in turn will be sensed by mechanosensitive ion channels. Fibrosis is not only accompanying cancer. The altered mechanics – sensed by mechanosensitive channels – can also lead to a feedforward, growth factor- and cytokine-mediated mutual activation of tumor and stromal cells, e. g. in PDAC and many other cancer types [138]. Myofibroblasts are found in invasive and metastatic carcinoma [139], and were postulated to induce tumor progression and even metastasis [140].

7. K_{2P} channels in cancer

Thus far, there are only few studies addressing the functional role of the mechanosensitive K^+ channels $K_{2P}4.1$ (TRAAK), $K_{2P}2.1$ (TREK1), and $K_{2P}10.1$ (TREK2) in cancer. Searching the publicly accessible online cancer microarray database "Oncomine" revealed a distinct expression pattern of K_{2P} channel mRNAs in frequently diagnosed cancer types [141]. Expression of a given channel can be upregulated in one cancer type, while it is downregulated in an other cancer. Thus, $K_{2P}2.1$ expression is elevated in lung cancer, but decreased in breast, gastrointestinal as well as head and neck cancer. $K_{2P}10.1$ expression is downregulated in colorectal and renal clear cell carcinoma. Expression changes of $K_{2P}4.1$ do not reach the threshold defined by the authors. However, it has to be kept in mind that a "negative "finding in this type of analysis neither means that mechanosensitive K_{2P} channels are absent nor functionally irrelevant in the respective cancer types. $K_{2P}2.1$ channels, for example, are expressed in prostate cancer but not found in normal prostate epithelial cells as shown by immunostaining, Western blot and patch clamp experiments. Their activity strongly correlates with proliferation and cell cycle progression [142,143]. The same observation was made for $K_{2P}10.1$ channels in 253 J bladder cancer cells [144]. $K_{2P}10.1$ channels are expressed at similar levels in normal ovaries and ovarial cancer, while that of $K_{2P}2.1$ channels is higher in cancer samples. The expression level of both channels in cancer samples has no predictive power with respect to patient survial. $K_{2P}2.1$ channel inhibition was said to impair ovarial cancer cell proliferation [145]. However, this interpretation was based on data with the fairly unspecific channel blocker curcumin which also inhibits other channels involved in cell proliferation such as $K_V1.3$ [146] and $K_V11.1$ [147], both of which are expressed in ovary cancer as well [148,149]. Finally, PDAC cells (BxPC-3) also express $K_{2P}2.1$ channels which contribute to cell proliferation and cell migration [150].

These examples reveal that mechanosensitive K_{2P} channels contribute to the aggressive cancer cell behavior. Yet, they do not allow to conclude that $K_{2P}2.1$, 4.1 and 10.1 channels do so because of their function of sensing or transducing mechanical stimuli. The mechanosensitivity of $K_{2P}2.1$ in ovary cancer cells was shown, but it was not related to its assumed role in proliferation [145]. On the other hand, it is conceivable that channels like $K_{2P}2.1$ channels become activated during migration [150] because of their function as mechanosensors and contribute to coordinating the movement of the front and rear ends of migrating cells [151]. Clearly, more experiments are needed to ascribe the impact of mechanosensitive K_{2P} channels on tumor cell behavior to their mechanosensitivity. This is likely to be a challenging task because this channel family is regulated by a multitude of other stimuli that can arise from the tumor microenvironment. The pH sensitivity of these channels [150] is just one example.

Potentially, $K_{2P}2.1$ channels can indirectly modify the mechanical properties of tumor microenvironment. In a model of pressure overload–induced cardiac dysfunction it was observed that the development of cardiac fibrosis depends on $K_{2P}2.1$ channels in fibroblasts. Moreover, *in vitro* scratch closure of $K_{2P}2.1^{-/-}$ fibroblasts and *in vivo* cutaneous wound healing in $K_{2P}2.1^{-/-}$ mice are impaired, pointing to a reduction in fibroblast proliferation and migration [152]. Whether this applies to the fibrosis found in many tumors remains to be determined. We found $K_{2P}2.1$ channels also in pancreatic stellate cells which produce massive amounts of extracellular matrix and cause the fibrosis in PDAC. $K_{2P}2.1$ expression seems to be regulated by the ambient pressure [12]. Their function in pancreatic stellate cells, however, still needs to be determined.

Taken together, the available evidence suggests that mechanosensitive K_{2P} channels contribute to shaping the aggressive tumor cell behavior. Whether they do so by sensing the mechanical or chemical properties of the tumor microenvironment is not yet clear. In addition, it is conceivable that they are indirectly modify the mechanical properties of the tumor microenvironment by stimulating fibroblast

Table 1
Function of mechanosensitive ion channels in cancer.

Channel	Selectivity	Main gating trigger	Mechano-sensitivity	Cancer types	Described roles in cancer
ANO1	Cl^-	Voltage, Ca^{2+} [175,176,177]	indirect [165]	gastric [178], PDAC [179], head and neck [180], oral [181], esophageal [182], colorectal [183], lung [184]	epithelial-mesenchymal transition, cell migration, viability, proliferation [166,185]
ASIC2	cations	H^+ [186]	indirect [156]	breast [187], glioblastoma [188], colorectal [189], lung [190]	cell proliferation, migration, invasiveness, reactive oxygen species production, metastatic spread [189,190]
CFTR	Cl^-	ATP [191]	direct [167]	lung [171], prostate [169], ovarian [173], breast [170], gastrointestinal [172], nasopharyngeal [174]	epithelial-mesenchymal transition, cell adhesion, invasiveness viability, angiogenesis, proliferation [192]
Cx46	non-selective	Voltage, Ca^{2+} [193]	direct [158]	breast [194], glioblastoma [195]	response to hypoxia, self-renewal of cancer stem cells [194,195]
$K_{2P}2.1$	K^+	Mechanical stress [21]	direct [24]	prostate [142,143], ovarian [145], PDAC [150]	cell cycle progression, cell proliferation, migration [142,143,150]
$K_{2P}10.1$	K^+	Mechanical stress [196]	direct [24]	bladder [144], ovarian [145]	cell cycle progression, cell proliferion [144,145]
$K_{Ca}1.1$	K^+	Voltage, Ca^{2+} [197]	direct [115], indirect [117]	prostate [114], breast [198], lung [119], glioblastoma [120]	cell invasiveness, cell cycle progression, metastatic spread [118,198]
$K_{Ca}3.1$	K^+	Ca^{2+} [199]	indirect [77]	breast [77], lung [200], PDAC [123], ovarian [201]	epithelial-mesenchymal transition, cell proliferation, migration, viability, immune avoidance, metastatic spread, fibrosis, angiogenesis, tumor immune response [202]
$Na_v1.5$	Na^+	Voltage [203]	direct [155]	breast [204], ovarian [205]	cell migration, invasiveness, metastatic spread [204]
NMDA-R	cations	Glutamate/glycine [206]	direct [207]	breast [208], lung [209]	cell cycle progression, cell proliferation, invasiveness [208,210]
$P2X_7$	cations	ATP [211]	indirect [162]	melanoma [212], skin squamous cell [213], colorectal [214], prostate [215], cervical [216], breast [217], leukemia [218]	cell viability, proliferation, metastatic spread [219]
Piezo1	cations	Mechanical stress [33]	direct [33]	lung [48], breast [40], gastric [41], bladder [42], osteosarcoma [43], synovial sarcoma [44]	tumor cell migration and proliferation [40,41,43]
Piezo2	cations	Mechanical stress [33]	direct [33]	glioblastoma [50]	tumor angiogenesis [50]
TRPA1	cations	Polymodal (Mechanical stress, temperature, chemical irritants) [220]	direct [64]	breast, lung [73]	cell adhesion, invasiveness, viability, oxidative stress tolerance [71,72]
TRPC1	cations	possibly Ca^{2+} store depletion [221,222]	direct [223]	breast [74,77], PDAC [76,82], glioblastoma [80,81], thyroid, nasopharyngeal [79]	epithelial-mesenchymal transition, cell migration, chemotaxis, invasiveness, proliferation [12,76,79,81,224]
TRPC6	cations	possibly diacyl-glycerol [225]	direct [226]	glioblastoma [84], prostate [85], esophageal [86], lung [87], PDAC [88]	angiogenesis, cell proliferation, invasiveness, fibrosis [84,87,88]
TRPM7	cations	Mg^{2+} [227], PIP_2 [228]	indirect [229]	lung [103], breast [104], melanoma [107], ovarian [109], PDAC [111], nasopharyngeal [113]	epithelial-mesenchymal transition, cell proliferation, migration, invasiveness [105,108,109,110,112]
TRPV4	cations	Polimodal (Mechanical [230] and osmotic stress [231], temperature [232], PIP2 [233])	direct, indirect [90,234]	gastric [94], breast [95], lung [91]	angiogenesis, cell proliferation, migration, invasiveness [91,93,95]

proliferation and migration.

8. Other channels

Besides the w ell-described candidates of mechanosensitive ion channels in the chapters above, there is a plethora of other channels recently recognized as being at least partially sensitive to mechanical stimuli. For further information see Table 1 and [153].

They include the voltage-gated potassium channel $K_V1.1$ [154], the voltage-gated sodium channel $Na_V1.5$ [155], the acid-sensitive ion channel ASIC2 [156], the ATP-gated $P2X_4$ and $P2X_7$ receptors [157] as well as the connexins (Cx46) forming the gap junctions [158]. However, there is no information to date about their mechanosensitive properties being related to the pathogenesis of neoplastic diseases. $P2X_7$ receptors are well known to play a role in tumor and stromal cells [159–161]. It is known that they can be indirectly activated by mechanically induced ATP release [162]. The relative importance of this mechanism for the elevated ATP concentration in the tumor microenvironment remains to be determined.

Mechanosensitive anion channels and their functional aspects in cancer are seemingly less well described. The volume-regulated anion channels (VRACs) play essential roles in cell volume regulation and in a multitude of other physiological functions as well as in cancer [163]. The alias of the channel, SWELL1, may imply that it is directly activated by mechanical cues due to swelling of the cell, but in reality, the channel is more likely to be activated by decreased intracellular ionic strength than direct mechanical stretch, as thoroughly described in [164]. The Ca^{2+}-activated Cl^--channel ANO1 (TMEM16A) has been pointed to play an indirect role in sensing fluid shear in biliary secretion [165], but so far it has not yet been tested whether this property is related to its role in cell migration [166].

In fact, the only chloride channel described as being directly responsive to membrane stretch is the cystic fibrosis transmembrane regulator (CFTR) [167]. CFTR dysfunction is widely known to cause cystic fibrosis, but not exclusively - a range of extrapulmonary diseases has been recently reviewed in [168]. Dysregulation of the CFTR has a critical pathophysiological role in the development, progression and metastasis of a wide range of cancers, including breast, lung, gastrointestinal, ovarian, prostate as well as nasopharyngeal cancers [169–174]. However, whether mechanosensitive properties of CFTR play a pathophysiological role in cancer remains to be elucidated.

In the recent years, more and more ion channels are characterized as being at least partially responsive to mechanical stimuli. Therefore, it would be not surprising, if more channels were added to list in the near future.

9. Outlook and conclusion

Tumor cells can sense changes in their mechanical environment and respond to these cues in a precise manner (Fig. 2). As obvious from the previous chapters, mechanosensitive ion channels are indispensable tools for the cancer and stroma cells to sense various forms of mechanical stress that affect them. Depending on the channel type, some can sense only specific forms of stimuli (e. g. $K_{Ca}1.1$ channels associated to focal adhesions) or may respond to a broad range of mechanical impulses (e. g. Piezo channels) [37,116]. Residing in the cell membrane, ion channels equipped with specific domains, such as ankyrin repeats in case of TRPA1, can be gated directly by mechanical stretch that is mediated by changes in the biophysical properties of the lipid bilayer [64]. In a larger group of mechanosensitive ion channels, the mechanism of sensing mechanical cues is still largely unclear. Regardless of the exact mechanism of mechanosensing, it is unclear whether the mechanosensory function itself would have functional consequences in cancer cells. In many studies, it has not been explicitly described (e. g. by durotaxis, intracellular calcium measurements) whether the absence of mechanosensitive ion channels would render cancer cells to become unresponsive to mechanical stimuli.

Mechanosensitive ion channels, besides sensing mechanical cues, are invaluable for cancer and stroma cells to respond to mechanical stimuli (Fig 2). These responses include cell migration, proliferation, tissue invasion or, in case of (myo-)fibroblasts, tumor fibrosis. As seen in the chapters above, all mechanosensitive ion channels have been heavily linked with these functions. However, in many studies detailed in this review, the direct link from the mechanosensitive function to the appropriate cellular response is missing. Providing this link would be crucial, as these channels are also regulated, at least partly, by other means than mechanical stress.

In this review we propose that ion channels are at the basis of another feedforward cycle culminating in altered tumor mechanics. The $K_{Ca}3.1$ channel drive fibroblast proliferation and matrix secretion in fibrosis. Increased matrix stiffness in fibrotic tumor areas stimulate mechanosensitive channels which can lead to a further activation of stroma and/or cancer cells or which maintain their state of activation. Activated tumor stroma cells secrete more matrix proteins and the cycle is closed (Fig 2). Thus, therapeutic ion channel targeting could be an attractive therapeutic concept to interrupt the above described vicious cycle.

Alleviating mechanical stress in tumors may not only inhibit fibrosis, but also stop tumor growth. Inhibition or knock-down of mechanosensitive ion channels can inhibit tumor growth and vascularization *in vivo*. This indicates that mechanosensitive ion channels are promising therapeutic targets for cancer. It can be anticipated that the recently published molecular structures will give rise to a new generation of more specific modulators of the channels. However, due to their ubiquitous expression in the body, the array of side effects *in vivo* needs to be evaluated with great care.

In conclusion, mechanical properties of the cancerous tissue are at least as dramatically altered as changes in the chemical milieu. Significant progress has already been made in linking cancer to the function of mechanosensitive ion channels. How exactly these channels translate the changes in tissue mechanics into cellular responses and vice versa, needs to be unveiled to get a better understanding in cancer pathophysiology.

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