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REVIEW

TRP channels and STIM/ORAI proteins: sensors and effectors of cancer and stroma cell migration

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Cancer cells are strongly influenced by host cells within the tumour stroma and vice versa. This leads to the development of a tumour microenvironment with distinct physical and chemical properties that are permissive for tumour progression. The ability to migrate plays a central role in this mutual interaction. Migration of cancer cells is considered as a prerequisite for tumour metastasis and the migration of host stromal cells is required for reaching the tumour site. Increasing evidence suggests that transient receptor potential (TRP) channels and STIM/ORAI proteins affect key calcium-dependent mechanisms implicated in both cancer and stroma cell migration. These include, among others, cytoskeletal remodelling, growth factor/cytokine signalling and production, and adaptation to tumour microenvironmental properties such as hypoxia and oxidative stress. In this review, we will summarize the current knowledge regarding TRP channels and STIM/ORAI proteins in cancer and stroma cell migration. We focus on how TRP channel or STIM/ORAI-mediated Ca^{2+} signalling directly or indirectly influences cancer and stroma cell migration by affecting the above listed mechanisms.

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Abbreviations
ECM, extracellular matrix; ER, endoplasmatic reticulum; HIF-1α, hypoxia-inducible factor-1α; IP_3, inositol-1,4,5 triphosphate; NAD, nicotinamide adenine dinucleotide; ORAI1, calcium release-activated calcium channel protein 1; ROCE, receptor-operated calcium entry; RTK, receptor tyrosine kinase; SOCE, store-operated calcium entry; STIM1, stromal interaction molecule 1; TME, tumour microenvironment; TRP, transient receptor potential

Introduction

Cell migration is fundamental to cell and tissue homeostasis and plays a pivotal role in many physiological and pathophysiological processes. Thus, wound healing, immune surveillance and angiogenesis require the migration of fibroblasts, immune cells and endothelial cells respectively (Stupack and Cheresh, 2004; Martin and Leibovich, 2005; Friedl and Weigelin, 2008; Silva, 2010). However, there are also a number of pathologies that involve 'too much' migration of the 'wrong' cell types. This is particularly relevant for cancer progression. The migratory activity of tumour cells is a critical step within the metastatic cascade that leads to the settling of tumour cells in distant organs (Yamaguchi *et al.*, 2005; Gupta and Massague, 2006; Hanahan and Weinberg, 2011). However, tumour cells do not act by themselves to acquire this aggressive migrating phenotype. They are strongly influenced by the tumour microenvironment (TME) and stromal cells of the host organ (e.g. fibroblasts, macrophages and other immune cells or endothelial cells). Tumour

stroma cells can therefore be viewed as an active partner in promoting cancer metastasis (Gupta and Massague, 2006; Joyce and Pollard, 2009; Brabek *et al.*, 2010). In fact, stroma cells are also found in metastases (Xu *et al.*, 2010).

In recent years, it has become evident that proteins involved in ion transport are involved in the mechanisms underlying the metastatic cascade and the tumour–stroma interaction (Fraser and Pardo, 2008; Arcangeli, 2011; Pedersen and Stock, 2013). Calcium signalling plays a particularly prominent role in regulating cancer and stroma cell functions including cell migration (Prevarskaya *et al.*, 2011; 2014; Chen *et al.*, 2013a).

Specifically, transient receptor potential (TRP) channels (see Alexander *et al.*, 2013a) and the protein complex consisting of the stromal interaction molecule (STIM) and calcium release-activated calcium channel protein (ORAI) have evolved as new players in this context (Bodding, 2007; Prevarskaya *et al.*, 2011; Bergmeier *et al.*, 2013; Ouadid-Ahidouch *et al.*, 2013). However, the molecular mechanisms by which they affect cancer and stroma cell migration as well as the mutual communication between these cell types are still far from being fully understood. The present review will focus on the role of TRP channels and STIM/ORAI proteins in regulating the mutual interplay between cancer and stroma cells with emphasis on cell migration. TRP channels are particularly interesting in this context since they are able to sense and respond to microenvironmental changes occurring during cancer development and progression. Further, we will discuss the role of STIM/ORAI proteins because they are also part of many of the growth factor signalling cascades underlying the tumour–stroma interplay. We refer to recent reviews for a comprehensive overview on the role of other ion channels and transporters in cell migration (Schwab *et al.*, 2012; Stock *et al.*, 2013; Schwab and Stock, 2014).

The tumour microenvironment (TME)

The progression of cancer requires genetic instability and a highly selective local TME. We therefore have to determine the environmental changes and corresponding adaptive cellular responses of cancer cells to explain their aggressive migrating phenotype (Gillies *et al.*, 2012). This includes processes shown in Figure 1, which either depend on migration of tumour and stroma cells or that regulate their migratory activity. During tumour progression, the stroma evolves over time to actively support tumour growth. It can form up to 90% of total tumour volume as observed in pancreatic ductal adenocarcinoma (PDAC) (Li *et al.*, 2010; Neesse *et al.*, 2011). This excessive amount of PDAC stroma, also known as desmoplasia, is the result of a massive deposition of the extracellular matrix (ECM) components (predominantly collagen I) from constitutively active fibroblasts and so-called stellate cells (Bachem *et al.*, 2005; Masamune *et al.*, 2008). Desmoplasia leads to poor vascularization and thereby to the development of a progressively hypoxic and acidic environment, which further increases tumour aggressiveness, in part via

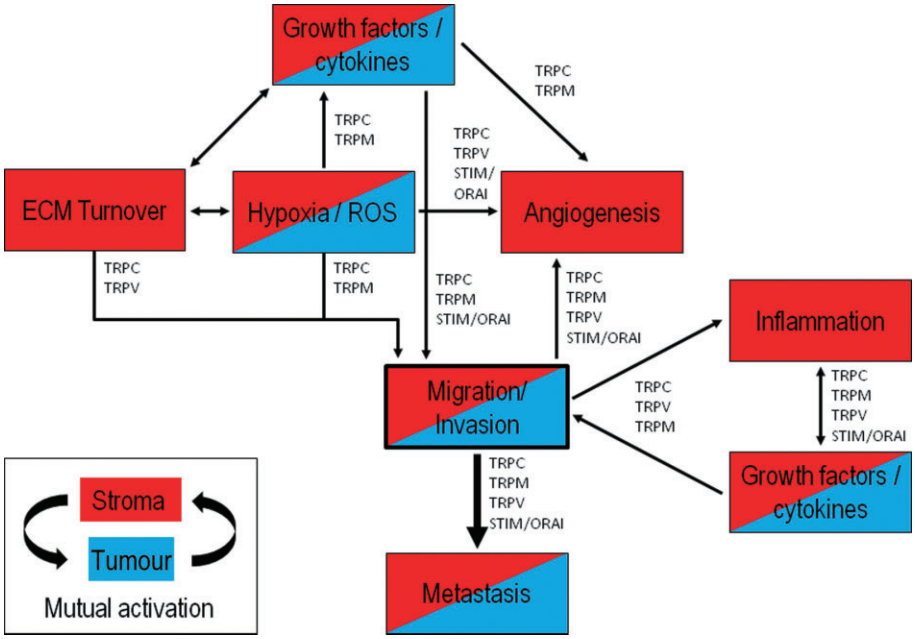

Figure 1

Major mechanisms of the tumour–stroma interplay in cancer progression. This illustration depicts major mechanisms in tumour progression involving either cancer cells (blue), stroma cells (red) or both (red/blue), all at some point being connected to cell migration. During tumour progression, cancer and stroma cells undergo a close mutual interaction with each other through continuous growth factor signalling. This shapes the tumour microenvironment and induces hypoxia and cellular oxidative stress, inflammatory responses, angiogenesis and ECM production/remodelling. The contributions of TRP channel families and STIM/ORAI proteins to different aspects of the cancer–stroma interplay underlying tumour invasion and metastasis are indicated.

hypoxia-inducible factor-1α (HIF-1α) and reactive oxygen species (ROS) signalling (Apte *et al.*, 2004; Masamune *et al.*, 2008; Webb *et al.*, 2011; Erkan *et al.*, 2012). A number of transport (and associated) proteins involved in stroma and tumour cell migration are HIF-1α-dependently up-regulated (Ivanov *et al.*, 2001; Koukourakis *et al.*, 2006; Tajima *et al.*, 2006; Lauritzen *et al.*, 2012). So far, there are only few reports on a similar HIF-1α dependence of TRP channel expression in tumours (Chigurupati *et al.*, 2010).

The mutual interplay between cancer and stroma cells

Three classes of stromal cells can be distinguished: angiogenic vascular cells, cancer-associated fibroblastic cells and infiltrating immune cells (Shimoda *et al.*, 2010; Hanahan and Coussens, 2012) such as tumour-associated macrophages and tumour-associated neutrophils (Joyce and Pollard, 2009; Roussos *et al.*, 2011). One common feature of stroma cells is their ability to migrate, which enables them to reach the tumour site and then recruit more cells to the tumour area such as immune cells. At the same time, it supports migration of cancer cells during the metastatic cascade (Kalluri and Zeisberg, 2006; Fukuda *et al.*, 2012).

The crosstalk between cancer and stroma cells largely depends on growth factors and cytokines secreted by both cell types (Joyce and Pollard, 2009; Sleeman *et al.*, 2012). They act in an auto and paracrine way and lead to the mutual activation of tumour and stroma cells in the sense of a positive feedback loop. Prominent examples of TME-associated growth factors include the EGF, PDGF and VEGF families. They are complemented by different interleukins and chemokines predominantly secreted by immune cells (Mantovani *et al.*, 2002; Bhowmick *et al.*, 2004; Allavena *et al.*, 2011). Growth factors are frequently released by matrix metalloproteinase (MMP) from ECM proteins to which they are bound (Li *et al.*, 2007; Barkan *et al.*, 2010; Kessenbrock *et al.*, 2010). Binding of these factors to their receptors can lead to the activation of TRP channels and/or STIM/ORAI proteins and the initiation of (local) intracellular Ca^{2+} signalling cascades (Gkika and Prevarskaya, 2009; Tajeddine and Gailly, 2012; Lindemann *et al.*, 2013). Sustained growth factor signalling of tumour and stromal cells culminates in the activation of the TME with induction of angiogenesis, ECM production/remodelling, sustained proliferation, tumour-promoting inflammation and migration/invasion. These processes can be linked to the functional expression of TRP channels and STIM/ORAI proteins as regulators of tumour and stroma cell migration (see Figure 1) (Wyckoff *et al.*, 2004; Joyce and Pollard, 2009; Brabek *et al.*, 2010; Chen *et al.*, 2013a; Fioro and Gkika, 2013; Prevarskaya *et al.*, 2014).

The discovery of the ability of stroma cells to co-metastasize to distant organs (Xu *et al.*, 2010) and their possible role in guiding invasive cancer cells through the ECM has further highlighted the significance of the migration of stroma cells (Friedl and Wolf, 2009; Friedl and Alexander, 2011). Thus, in an *in vitro* setting, collective invasion of squamous cell carcinoma cells depended on the presence of fibroblasts. They created cell tracks within the matrix for the cancer cells to follow (Gaggioli *et al.*, 2007). Breast cancer cells and macrophages employ a paracrine loop consisting of CSF-1 produced by carcinoma cells and EGF from macrophages to drive cell migration and invasion (Goswami *et al.*, 2005). Finally, we would like to point out that activation of stroma cells within the tumour can also lead to altered ion channel expression. This is exemplified in a breast cancer-derived endothelial cell line (BTEC). In these cells, the expression of TRPV4 channels that are involved in tumour angiogenesis was significantly higher than in endothelial cells derived from normal breast tissue (Fiorio *et al.*, 2008; 2012).

Calcium-dependent signalling in cell migration

Polarization along the axis of movement together with cytoskeletal and membrane dynamics is fundamental for cell motility regardless of the respective (patho-) physiological function (Nabi, 1999; Pollard and Borisy, 2003; Anderson *et al.*, 2008; Le Clainche and Carlier, 2008; Keren, 2011). This is in part mediated by a gradient of the intracellular calcium concentration ($[Ca^{2+}]_i$) within migrating cells with $[Ca^{2+}]_i$ being higher at the rear end than at the front (Brundage *et al.*, 1991; Schwab *et al.*, 1997). It allows different components of the cellular migration machinery including focal adhesions, receptors and ion channels to be functional either at the cell front or rear end (Eddy *et al.*, 2000; Broussard *et al.*, 2008; Schwab *et al.*, 2012; Stock *et al.*, 2013). In addition, the front-rear Ca^{2+} gradient can be superimposed by locally elevated Ca^{2+} zones and short-lived Ca^{2+} flickers that play a role in regulating the directionality of migrating cells (Fabian *et al.*, 2008; Wei *et al.*, 2009; Tsai and Meyer, 2012). In that way, cells are able to fine-tune their molecular repertoire to the local microenvironment and extracellular guidance cues (Friedl and Wolf, 2009). Numerous components of the cellular migration machinery are Ca^{2+} sensitive. They affect cytoskeletal remodelling, focal adhesion turnover, matrix degradation, leading edge guidance or localized cell volume changes (Schwab *et al.*, 2012; Falke and Ziemba, 2014). A rise of $[Ca^{2+}]_i$ can trigger the dynamic formation of lamellipodia through Rac1 and thereby increase migration or induce stress fibres through RhoA activity and inhibit cell migration (Etienne-Manneville and Hall, 2002; Singh *et al.*, 2007; Tian *et al.*, 2010). Ca^{2+} signalling induces (i) contraction of the actomyosin network (Yang and Huang, 2005); (ii) activation of calpain (Jang *et al.*, 2010), which is required for ECM matrix modelling by regulating MMP2 and 9 activity (Monet *et al.*, 2010; Sukumaran *et al.*, 2013), and regulation of focal adhesion turnover (Lawson and Maxfield, 1995; Giannone *et al.*, 2002; 2004; Wells *et al.*, 2005; Svensson *et al.*, 2010; Schafer *et al.*, 2012; Zhao *et al.*, 2012a); and (iii) induction of localized changes of the cell volume of migrating cells (Schwab *et al.*, 1995; Schneider *et al.*, 2000; Watkins and Sontheimer, 2011; Happel *et al.*, 2013). These examples show that cell migration can be seen as a Ca^{2+}-dependent signalling process, which can be linked to both Ca^{2+} influx through plasma membrane channels and/or Ca^{2+} release from internal Ca^{2+} stores.

TRP channels and STIM/ORAI proteins family

TRP channels are expressed ubiquitously throughout the body. They can be divided into subfamilies and subgroups based on amino acid sequence homology, mode of activation and function. The reader is referred to previous reviews on the subject (Pedersen *et al.*, 2005; Nilius and Owsianik, 2011). Most TRP channels are non-selective cation channels that are permeable to Ca^{2+} and Na^+ (P_{Ca}/P_{Na} = 1–10). Nonetheless, most studies dealing with TRP channels in cell migration related the functional impact of TRP channels to their Ca^{2+} permeability. For the purpose of this review, it is noteworthy that TRPM6 and TRPM7 are also Mg^{2+} permeable (Owsianik *et al.*, 2006).

TRP channels can be activated by diverse intra- and extracellular stimuli that are either of physical (e.g. temperature, osmotic pressure or mechanical stress) or chemical nature (e.g. pH, pO_2, ROS, neurotransmitters, growth factors/cytokines, environmental irritants). Several of these stimulants are characteristic for the TME (as discussed earlier). This enables TRP channels to act as multifunctional cellular sensors, which are in an ideal position to respond to the evolving physical-chemical composition of the TME during tumour progression (Chen and Barritt, 2003; Dietrich *et al.*, 2007; Bharate and Bharate, 2012). In this review, we will be focusing on members of the TRPC (Canonical), TRPV (Vanilloid) and TRPM (Melastatin) channel families as well as the STIM/ORAI complex (for nomenclature see Alexander *et al.*, 2013a). These channel families are attractive candidates for probing the TME because at least some of their members are exquisitely sensitive to components of the TME. For example, TRPC channels are part of GPCR and receptor tyrosine kinase (RTK) signalling cascades mediating receptor-operated calcium entry (ROCE) (Ambudkar and Ong, 2007), and members of the TRPM family such as TRPM2 are activated by oxidative stress that is frequently encountered in tumours (Ray *et al.*, 2012; Takahashi *et al.*, 2012; Tochhawng *et al.*, 2013).

Because GPCR signalling plays a central role in tumour pathophysiology, we will also address the role of the highly Ca^{2+}-selective STIM/ORAI proteins. GPCR activation leads to the production of inositol-1,4,5 triphosphate (IP_3) and Ca^{2+} release from intracellular stores into the cytosol. This, in turn, induces store-operated calcium entry (SOCE) (Minke and Cook, 2002; Clapham, 2003) mediated by STIM/ORAI proteins with STIM being the endoplasmatic reticulum (ER) Ca^{2+} sensor and ORAI the Ca^{2+}-selective Ca^{2+} entry channel (Soboloff *et al.*, 2006; 2012; Cahalan, 2009; Sours-Brothers *et al.*, 2009).

TRP channels and STIM/ORAI proteins functionally cooperate with other channels relevant for cell migration (Schwab *et al.*, 2012). On the one hand, they supply Ca^{2+}-sensitive channels such as $K_{Ca}3.1$, $K_{Ca}2.3$, CaCC (ANO/TMEM16) or ClC-3 with Ca^{2+} needed for their activation (Chantome *et al.*, 2013; Cuddapah *et al.*, 2013; Jacobsen *et al.*, 2013; Turner and Sontheimer, 2013; Wanitchakool *et al.*, 2014). On the other hand, TRP channels and STIM/ORAI proteins rely on the activity of K^+ channels that hyperpolarize the cell membrane potential in order to maintain the electrochemical driving force for Ca^{2+} entry (Gao *et al.*, 2010; Hammadi *et al.*, 2012). Such functional cooperation has been shown to be needed for efficient migration, invasion and metastases of different cell types (Hammadi *et al.*, 2012; Kuras *et al.*, 2012; Siddiqui *et al.*, 2012; Chantome *et al.*, 2013; Chimote *et al.*, 2013; Cuddapah *et al.*, 2013; Turner and Sontheimer, 2013).

TRP channels and the cytoskeleton

TRP channels are engaged in a reciprocal interplay with the cytoskeleton. TRP channels can control the intracellular milieu for cytoskeletal dynamics (Clark *et al.*, 2008). However, they can also be regulated by the cytoskeleton. For example, the interaction of TRPC1 channels with the calcium sensor STIM1 depends on an intact actomyosin cytoskeleton (Lopez *et al.*, 2006). Actin depolymerization with calyculin A was reported to induce the internalization of TRPC channels, thereby blocking calcium entry in human neutrophils (Itagaki *et al.*, 2004). TRPV1 and TRPV4 channels directly interact with actin and microtubule-enriched regions in larger signalling complexes synergistically regulating cell migration (Goswami *et al.*, 2006; 2010). The bidirectional regulation between TRP channels and the cytoskeleton mostly occurs through larger protein complexes in which TRP channels are linked to the actomyosin cytoskeleton, which thereby localizes signal transduction pathways and/or enhances the signal strength. These macromolecular protein complexes also include several signal transduction or scaffold proteins (Tang *et al.*, 2000; Clark *et al.*, 2006; Vandebrouck *et al.*, 2007; Smani *et al.*, 2013). Thus, Homer adaptor proteins are involved in the regulation of TRPC and ORAI channel gating in mammals (Yuan *et al.*, 2003; 2012; Jardin *et al.*, 2012). However, the functional role of Homer proteins in SOCE regulation and coupling to TRPC, STIM and ORAI is still debatable and might depend on the idiosyncrasy of the cellular models investigated. Dissociation of TRPC1 from Homer1 has been proposed to be essential for SOCE activation by allowing TRPC1 to interact with STIM1 in HEK 293 cells (Yuan *et al.*, 2003; 2012). In human platelets, SOCE requires the association of Homer1 with TRPC1 and the IP_3 receptor 2 (IP_3R2, for nomenclature see Alexander *et al.*, 2013b) together with its binding to STIM1 and ORAI1 (Jardin *et al.*, 2012). This enables regulation of TRP channels together with the STIM/ORAI complex at multiple levels, as interference of these macromolecular complexes can affect all its members together with downstream effectors involved in cell migration.

TRP channels and STIM/ORAI proteins as sensors and effectors of the TME

Being membrane proteins, TRP channels and STIM/ORAI proteins have the ability to sense and react to various intra- and extracellular stimuli known to occur in the TME. Major stimulants characteristic for the TME include (i) hypoxia and, as a consequence of the resulting oxidative stress, (ii) ROS and (iii) ADP ribose (ADPr) (Waris and Ahsan, 2006). Hypoxia is a typical feature of solid tumours. It is due to an imbalance

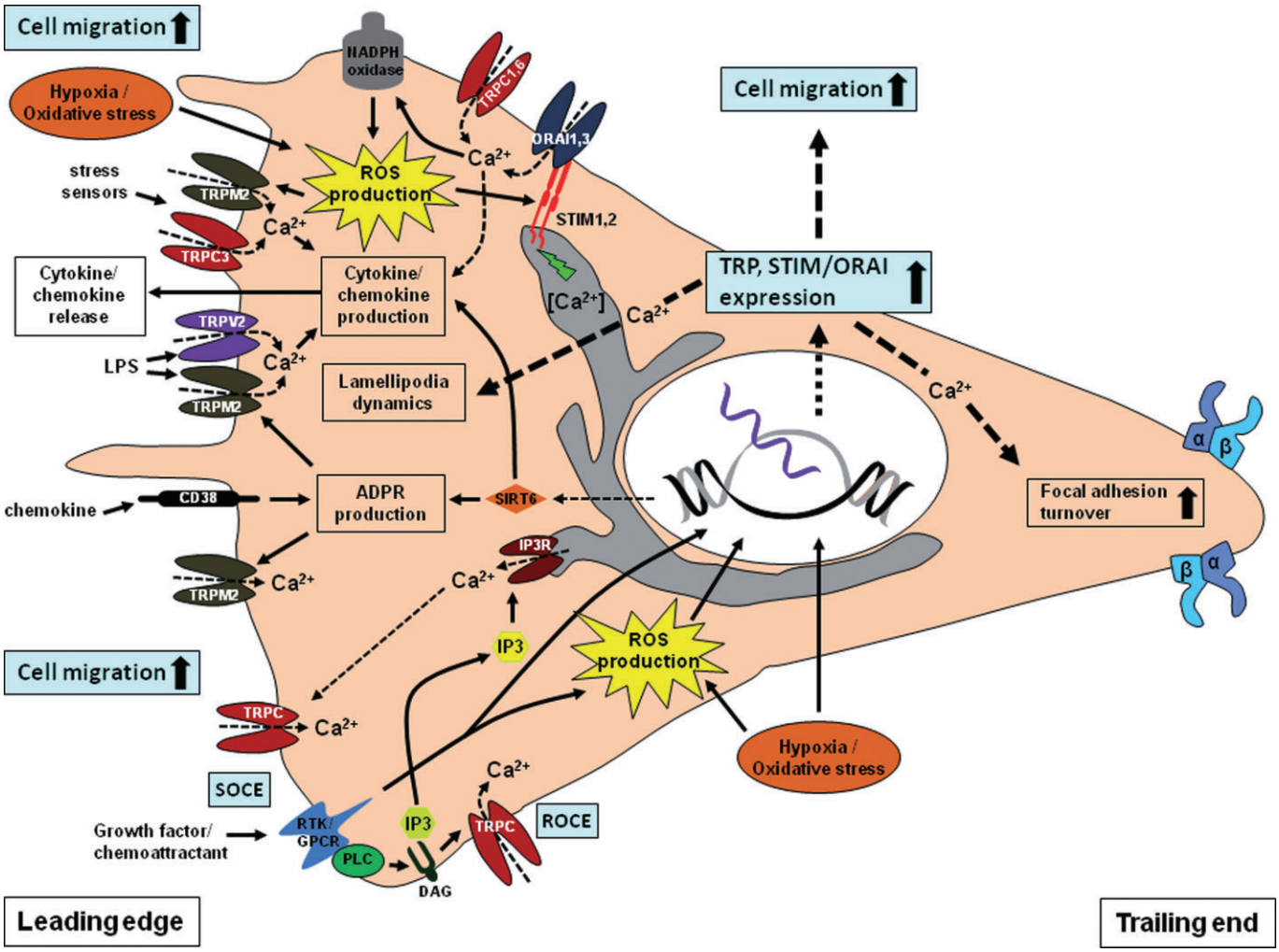

Figure 2

Multiple sensor and effector functions of TRP channels and STIM/ORAI proteins in the tumour microenvironment. Illustration of major hypoxia and cellular oxidative stress-dependent mechanisms in cancer and stroma cells involving TRP channels and STIM/ORAI proteins. Hypoxic and oxidative stress can lead to up-regulation of TRP channels (e.g. TRPC1, TRPC3 and TRPC6) and STIM/ORAI proteins and mediate the production of ROS and ADPr. In cancer and stroma cells, TRP channels and STIM/ORAI proteins can have both a sensor function for extra-/intracellular stimuli mediating cellular responses and a effector function by increased expression and activation to induce chemokine/cytokine production in these cells. For the sake of clarity, this sketch does not include all signalling pathways mentioned in the text. Neither did we include all microenvironmental, growth factor- and chemokine-activated pathways involved in increased activation or expression of TRP channels and STIM/ORAI proteins. (Figure modified from Stock *et al.*, 2013.)

between oxygen demand and insufficient vascularization as well as tumour anaemia (Hanahan and Weinberg, 2011; Webb *et al.*, 2011). So far, there is limited information about the impact of tumour hypoxia on TRP channel function although pO_2 is one of the environmental factors that are of particular importance for tumour progression. TRP channels can act both as sensors and effectors of the above-mentioned hypoxia-related stimuli by increasing their expression and/or activity and thereby mediate the respective cellular response (Numata *et al.*, 2013). These cell responses often involve elevated migratory activity and/or production/secretion of cytokines (illustrated in Figure 2) (Yamamoto *et al.*, 2008; Chigurupati *et al.*, 2010; Bauer *et al.*, 2012; Tochhawng *et al.*, 2013).

Recently, TRP channels were found to function as sensors of oxygen availability (see Numata *et al.*, 2013, for a review). TRP channels are either oxygen sensing themselves like TRPA1 channels in murine vagal and sensory neurons (Takahashi *et al.*, 2011), or their expression is regulated by pO_2 or their activity is indirectly regulated by pO_2. Acute hypoxic pulmonary vasoconstriction involves the activation of TRPC6 channels (Weissmann *et al.*, 2006) and the TRPC1-STIM1-ORAI1 complex is needed for regulating hypoxia-induced SOCE in pulmonary arterial smooth muscle cells (Lu *et al.*, 2008; Ng *et al.*, 2012). Hypoxic stress induces the expression of TRPM2 channels in cardiac fibroblasts leading to increased proliferation and ECM production (Takahashi *et al.*, 2012). In glioblastoma, expression of TRPC6 channels is

higher than in normal brain tissue. The elevated TRPC6 expression was replicated in *in vitro* experiments in which hypoxia increased TRPC6 channel expression in glioblastoma cells through a notch signalling pathway. Furthermore, suppression of TRPC6 greatly inhibited glioblastoma cell migration and invasion in response to hypoxia, possibly by inhibiting actin–myosin interactions (Chigurupati *et al.*, 2010).

Notably, hypoxia facilitates the production of ROS (Cook *et al.*, 2004; Waris and Ahsan, 2006; Yang *et al.*, 2013b). ROS often lead to oxidative stress and can also be generated as a result of growth factor stimulation of RTKs and thereby transmit signals to induce cellular changes necessary for migration by affecting several of the previously mentioned Ca^{2+}-sensitive effector molecules (Hurd *et al.*, 2011; Ray *et al.*, 2012; Tochhawng *et al.*, 2013). This points towards a coupling between ROS and Ca^{2+} ions as stress-response messengers. This coupling is mediated at least in part by TRP channels and STIM/ORAI proteins (Figure 2) (Hawkins *et al.*, 2010; Soboloff *et al.*, 2012; Numata *et al.*, 2013).

In PDAC cells, the expression of the NAD^+-dependent stress responsive protein sirtuin 6 (SIRT6) enhances the production of ADPr. Furthermore, ADPr triggers Ca^{2+} signalling mediated by TRPM2 channels that promote the expression of the pro-inflammatory factors IL-8 and TNF-α and enhance cancer cell migration (Bauer *et al.*, 2012). TRPM2, as well as TRPC3 channels, have also been demonstrated to serve as a sensor for oxidative stress in B-lymphoblasts which could enable the cells to reach or orient within the tumour (Roedding *et al.*, 2012). ROS-dependent activation of TRPM2 channels leading to IL secretion has also been observed in other immune cells such as monocytes and neutrophils (Yamamoto *et al.*, 2008; Wehrhahn *et al.*, 2010; Knowles *et al.*, 2011).

Hypoxic and pro-inflammatory conditions promote cellular stress and damage leading to an increase in intracellular NAD levels (Hong *et al.*, 2009). The ectoenzyme CD38, which is up-regulated in immune and cancer cells, mediates increased cADPr and ADPr generation from NAD (for a review, see Malavasi *et al.*, 2008; Vaisitti *et al.*, 2011). ADPr binds to the TRPM2 channel leading to Ca^{2+} influx (Partida-Sanchez *et al.*, 2007), which enhances the intracellular chemoattractant signal enabling chemotaxis of tumour and stroma cells (Vaisitti *et al.*, 2011). Additionally, neutrophil and monocyte chemotaxis to ligands for several chemokine and chemoattractant receptors, including CCR1, CCR2, CCR5, CCR7, CXCR4, *N*-formyl peptide receptor (FPR) 1 and FPR2 (for receptor nomenclature see Alexander *et al.*, 2013c), also requires CD38-dependent Ca^{2+} signalling (Partida-Sanchez *et al.*, 2001). In granulocytes, the inflammatory process of NADPH oxidase-mediated superoxide production could be related to TRPC1, TRPC3, TRPC6 and ORAI1 channels (Brechard *et al.*, 2008) (Figure 2). The activity of NADPH oxidase in ROS production is known to be relevant for cancer as well (Yang *et al.*, 2013b), and its activity has been observed to be regulated by growth factors in pancreatic cancer (Edderkaoui *et al.*, 2011). Taken together, these studies show that TRP channel expression and activity in both cancer and stroma cells is effectively regulated by ROS. The resulting cytokine/chemokine production can then support the recruitment of additional stroma cells. The chemosensitivity of TRP channels therefore probably constitutes an important element in securing the communication between stroma and cancer cells within the TME.

TRP channels in stroma cell migration

A substantial amount of data connects TRPC, TRPV and TRPM channels to stroma cell migration such as that of fibroblasts and immune cells like monocytes/macrophages, neutrophils and lymphocytes. Table 1 provides an overview of those TRP channels that are involved in stroma cell migration and cytokine/chemokine production. Some are illustrated in Figure 2.

Presently, it is assumed that the impact of most TRP channels on cell migration is due to their ability to mediate Ca^{2+} entry, for example, following the activation of growth factor or chemoattractant receptors (GPCR and RTK). Thereby, they are elements of the respective intracellular signalling cascades such as the phosphatidylinositol-3 kinase (PI3K) pathway, MAPK and the Ras-homologue-(Rho)-GTPases, which almost all depend on Ca^{2+} and affect cell migration (Falke and Ziemba, 2014). Rac and Cdc42 activation, for example, is regulated by guanine-nucleotide-exchange factors which can be activated by PI3K-mediated PIP_3 production and via an increase in the $[Ca^{2+}]_i$ (Benard *et al.*, 1999; Schmidt and Hall, 2002; Fukata *et al.*, 2003). PI3K activation could be linked to cytoskeletal reorganization, and ERK signalling regulates the actomyosin network by activation of Rho and myosin-II (Li *et al.*, 2013). Several studies showed that different TRP channels elicit their effect on migration of stromal cells via these pathways. Examples include TRPM7-dependent polarization and migration of fibroblasts (Su *et al.*, 2011), TRPC6-dependent chemotaxis of neutrophils towards ligands of the CXCR2 receptor (Damann *et al.*, 2009; Lindemann *et al.*, 2013), chemotaxis of monocytes towards fMLP relying on TRPC3 channels (Zhao *et al.*, 2012b) or TRPV2-dependent migration of macrophages (Link *et al.*, 2010).

In human neutrophils, platelet-activating factor-induced Ca^{2+} mobilization is prolonged by E-selectins in a TRPC6-dependent way (McMeekin *et al.*, 2006) pointing to a role of TRPC6 channels in neutrophil extravasation. Such a mechanism would also be relevant for tumour cells when leaving blood or lymph vessels at the site of metastasis. Finally, we already mentioned the role of TRPM2 in cell migration of neutrophils and monocytes which is mediated via CD38-mediated production of ADPr (Partida-Sanchez *et al.*, 2007; Vaisitti *et al.*, 2011).

Growth factor and cytokine secretion

TRP channel-dependent secretion of cytokines constitutes an indirect mechanism by which TRP channels contribute to the regulation of (directed) cancer and stroma cell migration. Thus, LPS triggers RAW264 macrophages to produce IL-6 and TNF-α upon Ca^{2+} entry via TRPV2 channels (Yamashiro *et al.*, 2010). Similarly, TRPM2 channels underlie enhanced cytokine/chemokine production in activated T-lymphocytes (Melzer *et al.*, 2012) and monocytes (Yamamoto *et al.*, 2008).

Table 1

TRP channels and STIM/ORAI proteins in stroma cell migration and function

Channel	Stroma cell type(s)	Function	Mechanism	Reference
TRPC1	HL-60 granulocytes	fMLP-mediated Ca^{2+} mobilization (TRPC1,3,6 and ORAI1) activates NAPD oxidase	ROS production	(Brechard *et al.*, 2008)
	Synovial fibroblasts	Stretch-mediated Ca^{2+} entry induces migration	Loss of TRPC1 decreases their mechanical stretch-induced change in the direction of migration	(Fabian *et al.*, 2012)
TRPC3	Human monocytes	Increased expression leads to increased Ca^{2+} mobilization, Akt and ERK signalling, and chemotaxis	Chemotaxis	(Zhao *et al.*, 2012b)
	BLCL lymphocytes	ROS diminishes channel expression	ROS sensor	(Roedding *et al.*, 2012)
TRPC6	Murine fibroblasts	Activation of p38 MAPK and SRF	Fibroblast-myofibroblast transformation	(Davis *et al.*, 2012)
	Murine neutrophils	Ca^{2+} mobilization regulates Akt and MAPK signalling	CXCR2-mediated chemotaxis	(Lindemann *et al.*, 2013)
	Human neutrophils	Channel activation via selectin signalling	Chemotaxis	(McMeekin *et al.*, 2006)
TRPV2	RAW264 macrophages	LPS induces TRPV2 Ca^{2+} mobilization leading to IL-6 and TNF-α production	Chemokine production	(Yamashiro *et al.*, 2010)
	Murine macrophages	Knock-down of TRPV2 impairs chemoattractant-elicited cell motility	Involved in phagocytosis and cell motility	(Link *et al.*, 2010)
TRPV4	Breast cancer-derived endothelial cells	Arachidonic acid-induced actin remodelling and increase in TRPV4 expression and function	Increased migration	(Fiorio *et al.*, 2012)
TRPM2	Human monocytes	LPS induces TRPM2 Ca^{2+} mobilization leading to IL-6, IL-9, IL-10 and TNF-α production	Chemokine production	(Wehrhahn *et al.*, 2010)
	T-lymphocytes	T-cell receptor triggering activates TRPM2	Cytokine secretion	(Melzer *et al.*, 2012)
	U937 monocytes	ROS induces TRPM2 Ca^{2+} mobilization leading to IL-8 production via ERK signalling	Chemokine production	(Yamamoto *et al.*, 2008)
	Murine T-cells	Regulation of IL-12 production	Cytokine production	(Knowles *et al.*, 2011)
	Murine neutrophils	CD38 triggered by ADPr production TRPM2 Ca^{2+} mobilization	Chemotaxis	(Partida-Sanchez *et al.*, 2007)
	BLCL lymphocytes	ROS diminishes TRPM2 channel activity	ROS sensor	(Roedding *et al.*, 2012)
TRPM4	Jurkat T-cells	Down-regulation of Ca^{2+} signalling and IL-2 production	Regulation of chemokine production	(Launay *et al.*, 2004)
	Murine T-cells	NFAT regulation	Migration and chemokine production	(Weber *et al.*, 2010)
TRPM7	3T3 fibroblasts	Rac and Cdc42 activation	Regulation of polarization and migration	(Su *et al.*, 2011)
	WI-38 fibroblasts	Ca^{2+} flickers at the leading edge regulate turning of the cells	Regulation of PDGF chemotaxis	(Wei *et al.*, 2009)
	Human T-cells	Ca^{2+} mobilization at the uropod	Cell migration	(Kuras *et al.*, 2012)
ORAI1	Human and murine neutrophils	SOCE during neutrophil transition from rolling to arrest	Recruitment and actin polarization in intravascular crawling	(Schaff *et al.*, 2010; Dixit *et al.*, 2011)
STIM1/ ORAI1	Murine T-cells	Involved in SOCE	Loss of expression leads to reduced cytokine production	(Gwack *et al.*, 2008; Oh-Hora *et al.*, 2008)
STIM1/2	Murine T-cells	STIM1 and STIM2 are critical for SOCE	Chemotaxis and cytokine production	(Ma *et al.*, 2010)
	Mast cells	STIM1 promotes the Ca^{2+} influx essential for mast cell activation and function	Lacking STIM1 leads to less degranulation and cytokine production	(Baba *et al.*, 2008)
	Murine lymphocytes	STIM1 functions as a redox sensor to constitutively activate ORAI channels under oxidative stress	Mitochondrial Ca^{2+} overload and alterations in cellular bioenergetics	(Hawkins *et al.*, 2010)

The overexpression of a dominant-negative mutant of TRPM4 or elimination of TRPM4 using RNAi in Jurkat T-cells induces enhanced Ca^{2+} signalling and increased IL-2 production (Launay *et al.*, 2004). In mouse T-cells, TRPM4 channels regulate the $[Ca^{2+}]_i$ in a similar way and affect cell motility and IL-2 as well as IL-4 production by controlling the nuclear translocation of nuclear factor of activated T-cells (Weber *et al.*, 2010). In addition, TRP channel activity itself can be regulated by cytokines. Myofibroblast transformation is supported by TRPC6 channels, which are activated by TGF-β (Davis *et al.*, 2012).

TRP channels in cancer metastasis and invasion

TRP channel expression is altered during cancer progression. In fact, TRPM1 was originally identified as a tumour-suppressor gene in melanoma so that increased TRPM1 expression was associated with reduced metastatic and migratory potential (Duncan *et al.*, 1998). Current knowledge indicates that increased or decreased TRP channel expression depends on the cancer type and cancer stage. TRP channels expression is particularly well studied in glioblastoma as well as in breast and prostate cancers. Even if their precise function has not yet been fully elucidated in all cancer types, their dysregulated expression represents a valuable diagnostic and/or prognostic marker. We refer to the following reviews for more details (Bodding, 2007; Prevarskaya *et al.*, 2007; Van Haute *et al.*, 2010; Santoni and Farfariello, 2011; Ouadid-Ahidouch *et al.*, 2013). TRP channels whose expression in tumour cells is frequently dysregulated include TRPC1 and 6, TRPM7, TRPM8, and TRPV2 and 6. Their expression strongly correlates with tumour aggressiveness in different cancer types, as observed in human breast ductal adenocarcinoma. TRPV6 is mainly overexpressed in the invasive breast cancer cells and not in the corresponding non-invasive ones. Down-regulating TRPV6 in two breast cancer cell lines, MDA-MB-231 and MCF-7, reduced cell migration and invasion (Dhennin-Duthille *et al.*, 2011). Table 2 provides an overview of those TRP channels that contribute to cancer cell migration.

In migrating glioblastoma cells, TRPC1 channels were detected in lipid rafts at the leading edge where they are needed for directed migration in an EGF gradient (Bomben *et al.*, 2011). Their mode of action in controlling directional migration was investigated in more detail in transformed renal epithelial (MDCK-F) cells (Fabian *et al.*, 2008; 2011; 2012). TRPC1 channels elicit a local Ca^{2+} microdomain at the leading edge. Its lack following TRPC1 ablation cannot be compensated for by external cues so that TRPC1-deficient MDCK-F cells are unable to chemotax towards FGF-2 (Fabian *et al.*, 2011). TRPC1 channels also mediate TGF-β-induced Ca^{2+} responses associated with migration in human PDAC cells (Dong *et al.*, 2010). Another member of the TRPC family, TRPC3, participates in two Ca^{2+} influx ways in MCF-7 breast cancer cells: SOCE and ROCE. Both ways are needed for cell migration so that their inhibition with polyunsaturated fatty acids impairs cell migration (Zhang *et al.*, 2012). TRPC6 channels are also highly expressed in head and neck squamous cell carcinoma tumour samples and cancer cell lines. Their down-regulation inhibits cell invasion and cell migration (Bernaldo de Quiros *et al.*, 2013). Moreover, in rat thyroid FRTL-5 cells, down-regulation of TRPC2 channels inhibits cell migration and invasion by decreasing Rac, calpain and MMP2 activity important for ECM remodelling (Sukumaran *et al.*, 2013; Zhang *et al.*, 2013).

TRPM7 channels are involved in migration of multiple cancers including lung cancer (Gao *et al.*, 2011), nasopharyngeal carcinoma (Chen *et al.*, 2010), breast cancer (Middelbeek *et al.*, 2012) and PDAC (Rybarczyk *et al.*, 2012). While the pro-migratory role of TRPM7 channels in nasopharyngeal carcinoma cells was linked to Ca^{2+} influx (Chen *et al.*, 2010), that in PDAC cells was due to Mg^{2+} influx (Rybarczyk *et al.*, 2012). TRPM7 has also been found to increase actomyosin reorganization and cell adhesion in spreading of N1E-115 neuroblastoma cells by cooperating with $K_{Ca}1.1$ channels (Clark *et al.*, 2006). In MDA-MB-231 breast cancer cells, TRPM7 regulates myosin-II-based cellular tension and thereby modifies focal adhesion number, cell-cell adhesion and polarized cell movement (Middelbeek *et al.*, 2012). TRPM7 knock-down increases focal adhesions and impairs migratory and metastatic properties of MDA-MB-231 and -435 breast cancer cells (Meng *et al.*, 2012; Middelbeek *et al.*, 2012). TRPM7 channels were therefore suggested to be part of a mechanosensory complex adopted by cancer cells to drive metastasis formation (Middelbeek *et al.*, 2012). This is a similar role as seen in fibroblast migration (Wei *et al.*, 2009) and for TRPC1 channels in MDCK-F cell migration (Fabian *et al.*, 2012).

A connection to $K_{Ca}1.1$ channels was also observed for TRPM8 in glioblastoma cell migration. Menthol and hepatocyte growth factor induced TRPM8-mediated Ca^{2+} influx, which further activated $K_{Ca}1.1$ channels important for sustaining increased glioblastoma cell migration (Wondergem *et al.*, 2008; Wondergem and Bartley, 2009). In contrast, increased expression of TRPM8 in PC-3 prostate cancer cells correlated with a decrease of migration efficiency via inactivation of focal adhesion kinase (Yang *et al.*, 2009b). Similarly, TRPM8 activation with prostate-specific antigen also decreased cell migration of PC-3 prostate cancer cells (Gkika *et al.*, 2010). Mice transplanted with TRPM8-overexpressing PC-3 cells developed tumours that were less vascularized than control (Zhu *et al.*, 2011). The apparently discrepant findings with respect to the role of TRPM8 channels in tumour cell migration could be either due to the different cell types (glioma vs. prostate cancer cells) or due to the expression of different TRPM8 isoforms in the plasma membrane and the ER (Gkika and Prevarskaya, 2009; 2011; Van Haute *et al.*, 2010).

In prostate cancer cells, lysophosphatidylcholine and lysophosphatidylinositol activate TRPV2 channels and thereby increase migration via the PI3,4K pathway (Monet *et al.*, 2009) and increased expression of MMP2, 9 and cathepsin B (Monet *et al.*, 2010). Similarly, adrenomedullin, a peptide originally isolated from human phaeochromocytoma (Kitamura *et al.*, 1993), stimulates prostate and urothelial cancer cell migration and invasion by increasing TRPV2 membrane expression and activity (Oulidi *et al.*, 2013). Activation of TRPV1 channels in human hepatoblastoma (HepG2) cells enhances migration, possibly via dynamic regulation of microtubules (Goswami *et al.*, 2006; Waning

Table 2

TRP channels and STIM/ORAI proteins in cancer cell migration

Channel	Cancer cell type(s)	Function	Mechanism	Reference
TRPC1	Glioblastoma	EGF-stimulated localization to leading edge in migration	Chemotaxis towards EGF	(Bomben *et al.*, 2011)
	MDCK-F cells	Inhibition or down-regulation affects cell polarization, FGF-2 chemotaxis and stretch activation	Chemotaxis towards FGF-2 involved in mechanosignalling	(Fabian *et al.*, 2008; 2011; 2012)
	BxPC3 PDAC cells	TGF-β-induced Ca^{2+} responses	Increased motility and invasion	(Dong *et al.*, 2010)
TRPC2	FRTL-5 thyroid cells	Regulates Rac and calpain activity	Down-regulation decreases cell migration	(Sukumaran *et al.*, 2013)
TRPC3	MCF-7 breast cancer cell	SOCE/ROCE function. Polyunsaturated fatty acids inhibit TRPC3.	Increased migration and invasion	(Zhang *et al.*, 2012)
TRPC6	Glioblastoma	Increased expression through hypoxia-induced notch signalling	Knock-down inhibits migration and invasion	(Chigurupati *et al.*, 2010)
	Head and neck squamous cell carcinomas	Increased expression in cell lines and tumour tissue	Knock-down inhibits invasion	(Bernaldo de Quiros *et al.*, 2013)
TRPV1	Hepatoblastoma(HepG2)	HGF increases TRPV1 channel activity	Increased migration	(Waning *et al.*, 2007)
TRPV2	PC3 and LNCaP prostate cancer cells	Lysophosphatidylcholine and lysophosphatidylinositol induced calcium influx by PI3,4K pathway	Increased expression and migration	(Monet *et al.*, 2009)
	PC3 xenograft tumours in mice		Induction of MMP2, MMP9 and cathepsin B	(Monet *et al.*, 2010)
	PC-3 prostate cancer cells and urothelial carcinoma cells T24/83	Adrenomedullin induced membrane expression followed by increased activity	Increase in migration and invasion	(Oulidi *et al.*, 2013)
TRPV4	Hepatoblastoma (HepG2)	Increased lamellipodial dynamics at frontal region of migrating cells	Increased migration	(Waning *et al.*, 2007)
TRPV6	MDA-MB-231 and MCF-7 breast cancer cells	Increased expression in non-invasive (MCF-7) and invasive (MDA-MB-231) cells	TRPV6 silencing reduced migration and invasion	(Dhennin-Duthille *et al.*, 2011)
TRPM1	B16-F1 melanoma cells	High expression in poor metastatic variants and increased expression in highly metastatic variants	Functional expression reduces metastasis and migratory potential and vice versa	(Duncan *et al.*, 1998)
TRPM2	BxPC-3 PDAC cells	Increased activation through SIRT6-elevated ADPr levels, an activator of TRPM2	Increased migration	(Bauer *et al.*, 2012)
TRPM7	N1E-115 neuroblastoma cells	Activation affects actomyosin contractility and cell adhesion	Increased cell spreading through BK channel activation	(Clark *et al.*, 2006)
	MDA-MB-435 breast cancer cells	TRPM7 modulation involving the Src-MAPK signalling pathway	Silencing TRPM7 reduces cell migration and invasion	(Meng *et al.*, 2012)
	MDA-MB-231 breast cancer cells	Polymerization of the cytoskeleton	Silencing TRPM7 impairs migratory and metastatic properties	(Middelbeek *et al.*, 2012)
	BxPC-3 PDAC cells	Increased expression in PDAC and contribution to $Mg2^{+}$ entry	Silencing TRPM7 reduced cell migration	(Rybarczyk *et al.*, 2012)
	5-8F and 6-10B nasopharyngeal carcinoma cells	Controlling $Ca2^{+}$ influx	Increased migration	(Chen *et al.*, 2010)
	A549 lung cancer cells	Basal and EGF-induced migration	Increased migration	(Gao *et al.*, 2011)

Table 2

Continued

Channel	Cancer cell type(s)	Function	Mechanism	Reference
TRPM8	Glioblastoma	Menthol and HGF/SF increases $[Ca2+]_i$ by activating TRPM8	Increased migration through BK channel activation	(Wondergem *et al.*, 2008; Wondergem and Bartley, 2009)
	PC-3 prostate cancer cells	Overexpression of TRPM8 inactivates focal adhesion kinase	Decreased migration	(Yang *et al.*, 2009b)
	PC-3 prostate cancer cells	PSA activated TRPM8 via the bradykinin 2 receptor signalling pathway	Decreased migration	(Gkika *et al.*, 2010)
STIM1/ORAI1/	Glioblastoma	Increased expression of both ORAI1 and STIM1	Increased migration	(Motiani *et al.*, 2013a)
	Hepatocellular carcinoma cells (HCC-LM3)	Regulate de-phosphorylation of focal adhesion kinase, and by that modulate focal adhesion turnover	STIM1 silencing and SOCE inhibitor inhibited migration and invasion	(Yang *et al.*, 2013a)
	MDA-MB-231 breast cancer cells and mouse tumour	Implicated in serum-induced migration. Modulate focal adhesion turnover through Ras and Rac1	Increased migration and invasion	(Yang *et al.*, 2009a)
ORAI1	Human breast cancer cell line MDA-MB-435s	Colocalized in lipid rafts with $K_{Ca}3.2$ to regulate Ca^{2+} influx and calpain activity	Involved in migration and bone metastases	(Chantome *et al.*, 2013)
STIM1/ORAI3/	MCF-7 breast cancer cells (ER^+ breast cancer cells)	EGF and thrombin mediated Ca^{2+} entry and ERK, focal adhesion kinase and NFAT regulation	Increase in tumourigenesis and invasion	(Motiani *et al.*, 2010; 2013b)

et al., 2007). Additionally, activation of the mechanosensitive TRPV4 channels led to increased lamellipodial dynamics pointing to the importance of the mechanosensitivity of the frontal region of migrating cells (Waning *et al.*, 2007). This observation was later supported in F11 neuroblastoma x DRG neuron hybrid cells, where TRPV4 interacted with polymerized actin and tubulin filaments (Goswami *et al.*, 2010).

STIM/ORAI in the tumour–stroma interplay

Several studies have addressed the role of STIM/ORAI proteins function in cells of the immune system (Feske, 2009; Chen *et al.*, 2013a; Shaw *et al.*, 2013). They showed, among others, that ORAI1 is required for the recruitment of neutrophils (Schaff *et al.*, 2010; Dixit *et al.*, 2011) or T-lymphocytes (Waite *et al.*, 2013) from the blood stream. Murine T-cells lacking STIM1 or ORAI1 show severe defects in the production of IL-2, IL-4 and IFN-γ (Gwack *et al.*, 2008; Oh-Hora *et al.*, 2008). In addition, STIM1 and STIM2 are critical for chemotaxis of T-cells and pro-inflammatory cytokine production (Ma *et al.*, 2010). STIM1 was also found to be a key factor in promoting Ca^{2+} influx essential for mast cell degranulation and cytokine production (Baba *et al.*, 2008).

These observations are relevant for mechanisms underlying anti-tumour immunity. For example, high lactate levels in tumours suppress the proliferation and cytokine production of tumour-specific $CD8^+$ cytotoxic T-lymphocytes (Fischer *et al.*, 2007). This study did not yet address the role of STIM/ORAI in this process. However, it was later found that $CD8^+$ T-cells lacking STIM1/2 have impaired SOCE leading to a defect in the anti-tumour immunity together with preventing tumour engraftment and growth (Weidinger *et al.*, 2013). Moreover, the above mechanisms may also be relevant for the extravasation of tumour cells at their site of metastasis and for the recruitment of inflammatory cells to the tumour stroma. Accordingly, silencing of ORAI1 impaired the extravasation of nasopharyngeal cancer cells in a zebrafish model (Zhang *et al.*, 2013). Indeed, altered expression and function of STIM/ORAI proteins in cancer cells is crucial for their behaviour and thereby for patient prognosis (McAndrew *et al.*, 2011). In several tumour cell types including human primary glioblastoma, as well as cervical, hepatocellular or breast cancer cells, STIM/ORAI proteins were found to control invasion and migration and thereby metastases (Motiani *et al.*, 2013a). At present, a likely explanation for these effects is the modulation of the turnover of focal adhesions by (local) regulation of the $[Ca^{2+}]_i$ (Yang *et al.*, 2009a; 2013a; Motiani *et al.*, 2010; 2013b; Chen *et al.*, 2011; 2013b). Interestingly, in breast cancer cells, ORAI1 colocalizes with $K_{Ca}2.3$ independently from STIM1 within lipid rafts promoting cancer cell migration and bone metastases (Chantome *et al.*, 2013).

Concluding remarks and clinical perspectives

Intracellular Ca^{2+} is one of the most versatile messengers regulating a plethora of cell functions including cell migration. It reflects the balance between Ca^{2+} influx and efflux across the plasma membrane as well as release from and uptake into intracellular stores. TRP and ORAI channels are important constituents of the Ca^{2+} influx pathways. Consequently, they are important regulators of Ca^{2+}-dependent functions of both cancer cells and their surrounding stroma cells, such as migration, growth factor production and adaptation to microenvironmental changes. Their prominent role in cancer development and progression can be related to the fact that the expressions of TRP channels and STIM/ORAI proteins are frequently dysregulated in cancer in a stage and cancer type-dependent manner (Van Haute *et al.*, 2010; Santoni and Farfariello, 2011; Ouadid-Ahidouch *et al.*, 2013). They share this property with many other ion channels such as K^+, Na^+ or Cl^- (Prevarskaya *et al.*, 2010; Britschgi *et al.*, 2013).

So far, there is only relatively limited information about TRP channels and STIM/ORAI proteins in tumour stroma cells. Despite a wealth of data on the function of ion channels in these cells, the elucidation of their role in cancer is still at its beginning. However, the observation that TRPV4 channel expression in tumour-derived endothelial cells differed from that in normal endothelial cells (Fiorio *et al.*, 2012) highlights the importance of investigating the composition of the transportome of tumour-derived stroma cells in more detail. Until now, we largely rely on 'proof of principle' studies performed in 'normal' stroma cells showing that TRP channels and STIM/ORAI proteins are central for migration and/or growth factor secretion. In this review, we therefore attempted to synthesize the available knowledge from mostly 'non-cancer' studies in order to point to the potential importance of TRP channels and STIM/ORAI proteins in tumour stroma cells. However, depending on the degree of dysregulation in the cancer stroma, their role may be over- or underestimated. Profiling of TRP channels and STIM/ORAI proteins in tumour stroma cells needs to be complimented by the identification of downstream effector molecules of the cellular migration apparatus. The elucidation of the roles of these channel families in regulating tumour and stroma cell migration and other pro-metastatic behaviour therefore still constitutes a novel area of future research in oncology.

Nonetheless, the current knowledge allows us to propose that TRP channels and STIM/ORAI proteins represent potential therapeutic, diagnostic and/or prognostic targets with clinical potential in oncology. This is in part due to the fact that they are not only involved in cell migration but also in other functions critical for cancer progression such as tumour cell proliferation. This has, among others, been observed for TRPC1 and TRPC6 in glioblastoma (Bomben and Sontheimer, 2010; Chigurupati *et al.*, 2010; Ding *et al.*, 2010; Bomben *et al.*, 2011), ORAI3 in breast cancer (Motiani *et al.*, 2010; 2013b), and TRPM8 and TRPV2 in prostate cancer (Yang *et al.*, 2009b; Monet *et al.*, 2010). Important functions of TRP channels within endothelial cells such as angiogenesis and vascularization of the tumour have also been observed (Fiorio *et al.*, 2008; 2012; Lodola *et al.*, 2012) (reviewed in Fioro and Gkika, 2013). Moreover, targeting TRP channels or STIM/ORAI proteins expressed in both cancer and stroma cells offers the potential for a 'double hit' and the potential to break the vicious cycle of mutual cancer and stroma cell stimulation. Their dysregulated expression and function in tumours may also confer some degree of specificity over those channels expressed in healthy organs. Finally, being membrane proteins, TRP channels or ORAI proteins are easily accessible from the extracellular side, which reduces the risk of multidrug resistance due to drug export from the cytoplasm. Thus, there is an urgent demand to develop specific modulators of TRP channels or STIM/ORAI proteins that would ideally target splice variants or differently expressed channels only found in cancer as observed for TRPM8 (Shimoda *et al.*, 2006).

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Conflict of interest

The authors do not have a conflict of interest.

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