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Review

Functional and physiopathological implications of TRP channels

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ABSTRACT

Transient Receptor Potential (TRP) channel proteins are a diverse family of proteins that are expressed in many organisms, tissues and cell types. TRP channels respond to a variety of stimuli, including light, mechanical or chemical stimuli, temperature, pH or osmolarity. In addition, several TRP family members have been identified as downstream molecules in the G protein-coupled receptor signaling pathway. TRP proteins are involved in a variety of cell functions both in non-excitable and excitable cells due to their diverse permeability to cations and their ability to modulate intracellular Ca^{2+} signaling. Emerging evidence suggests that TRP channel dysfunction significantly contributes to the physiopathology of a number of diseases, including cardiovascular, neurological, metabolic or neoplastic disorders. This review focuses on the implication of TRP proteins in the pathogenesis of some of the most prevalent disorders in human. We summarize the current findings regarding the role of TRP proteins in the development of cardiovascular disease, diabetes mellitus as well as diabetic complications, and tumorigenesis and present TRP proteins as targets of potential diagnostic and therapeutic strategies.

1. Introduction

Transient receptor potential (TRP) channels are a family of ion channels distantly related to voltage-gated superfamilies. TRP channels are expressed in a variety of organisms such yeasts, worms, flies and mammals, including human, where they play important cellular functions. TRP proteins were initially identified in *Drosophila*, where a spontaneously occurring mutation of the *trp* and *trpl* genes selectively abolish the delayed, light-sensitive and sustained depolarization due to Na^+ and Ca^{2+} influx in the photoreceptors [1]. As a consequence, the TRP *Drosophila* mutant showed a transient rather than sustained light-sensitive depolarization and receptor potential, which designated the name to these channels [2].

The metazoan TRP family has been subdivided into seven major groups: three major subfamilies closely related to *Drosophila* TRP (TRPC (canonical), TRPV (vanilloid), TRPA (ankyrin) and TRPM (melastatin)), two subfamilies that are more distantly related to TRP (TRPP (polycystin) and TRPML (mucolipin)), and a less related TRPN group (also known as NOMPC (no mechanoreceptor potential C) that has not been found in mammals but is expressed in flies and worms, and cold-blooded vertebrates (see [3,4]. In addition yeast and other fungi have been reported to express a TRP channel subfamily known TRPY (yeast) [4]. TRP proteins form ion channels mostly non-selective for monovalent and divalent cations, with some exceptions such as TRPM4 and TRPM5, which, unlike other TRP members, show a great selectivity for monovalent cations, and TRPV5 and TRPV6 that are highly selective for Ca^{2+}.

TRP channels have been shown to be gated by a variety of physical and chemical stimuli, including stretch, changes in temperature and a large number of endogenous (such as diacylglycerol or Ca^{2+}) or exogenous ligands. Some of them have also been reported to be activated by intracellular Ca^{2+}-store depletion [5,6].

Accumulating evidence have demonstrated that TRP channels play important roles both in physiological as well as pathophysiological processes. TRP channels function as receptor-operated, second-messenger operated or store-operated channels facilitating the influx of Na^+ and Ca^{2+}, which, in turn, contributes to membrane depolarization and the activation of Ca^{2+}-dependent mechanisms in a variety of systems and organs [7]. Furthermore, dysregulation of TRP channel function, which might include abnormal expression levels, cellular location or mutations, has been found associated to a large number of disorders, thus revealing the crucial biological relevance of these channels. In the present review we have focused on three of the most prevalent pathologies: cardiovascular disorders, diabetes mellitus and cancer, and their association with TRP channel dysfunction.

2. TRP channels in the cardiovascular system

Nearly all TRP channels (TRPs) are expressed in both excitable and non-excitable cells of the cardiovascular system (for reviews covering

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the cardiovascular system, see [8–10]). TRP proteins expression has been detected functionally by current recordings or by molecular biology techniques as RT-PCR, western blotting or immunostaining. TRPs can open upon direct ligand binding, G-protein coupled signalling, and membrane depolarization. Actually, they can sense a variety of different stimuli including pressure, oxidative stress, sheer stress, mechanical stretch, lipids, hypertrophic signals and inflammation products. TRPs are involved in several fundamental cardiovascular cell functions, as they integrate multiple stimuli and transduce their activity to downstream cellular signal pathways generally via Ca^{2+} entry and membrane depolarization. Thereby, TRPs play a crucial role in smooth muscle and cardiac myocytes contraction, relaxation, proliferation, differentiation, and cell death.

2.1. Role of TRP channels in the vascular system

Vascular smooth muscle cells (VSMCs) play a central role in controlling vascular tone and maintaining the integrity of vessel wall. Several reports have shown that TRP channels-mediated Ca^{2+} entry plays an important role in the regulation of vascular tone, mechano-sensing, angiogenesis, cell proliferation, and various vascular disorders [11–13].

2.1.1. Vascular tone regulation

Most of TRPs are expressed in blood vessels, especially in endothelial cells and vascular smooth muscle cells and they contribute to vascular tone regulation and myogenic response. Within TRP channels TRPC family is likely the mediator of receptor activation and the induced vascular constriction [11,12]. Indeed, TRPC1 has been suggested to contribute to store operated Ca^{2+} entry (SOCE) induced by endothelin-1 (ET-1) in caudal arteries [14]. Conversely, overexpression of TRPC1 in rat pulmonary artery enhanced SOCE-mediated vasoconstriction [15]. However, TRPC1 gene disruption did not attenuated aortic smooth muscle vasoconstriction [16,17]. Other agonists such as angiotensin II also stimulated both TRPC1 and TRPC6 in mesenteric artery [18]. Meanwhile, ET-1 also activated TRPC7 and TRPC3 in rabbit coronary artery [19]. TRPC6 was also implicated in α1-adrenergic receptor-induced Ca^{2+} entry [20] and in vasopressin-responses in A7R5 cells [21]. Moreover, the elimination of TRPC6 prevented acute hypoxic pulmonary vasoconstriction in TRPC6-null mice [22]. However and unexpectedly, TRPC6-KO mice exhibited elevated blood pressure and enhanced agonist-induced contractility in isolated tracheal [23], aortic rings and cerebral arteries [24], although these effects have been related to TRPC3, which is up-regulated in TRPC6-deficient mice [24].

Moreover, TRPs are also involved in myogenic responses and in stretch-activated channels (SAC), which respond to mechanical stress as well as cell swelling [25]. Independent studies have shown that TRPC6 or TRPM4 downregulation attenuated significantly the pressure-induced arterial smooth muscle depolarization and myogenic vasoconstriction of intact cerebral artery [26,27]. Nevertheless, genetic ablation of either *trpc6* or *trpm4* genes has little effect on the pressure-induced constriction of mice cerebral arteries [24,28]. Therefore, further investigation is required to resolve both channels role in mechano-sensitivity and myogenic tone regulation. Alternatively, two other TRP proteins, the polycystic kidney disease associated TRPP1 and TRPP2 also known as PKD1 and PKD2, were proposed as regulators of SAC in VSMCs [29]. Indeed, the mesenteric myogenic tone was significantly impaired in TRPP1-null mice, meanwhile the deletion of TRPP2 in TRPP1-deficient mice restored SAC activity and myogenic tone [29].

2.1.2. VSMC growth and vascular remodelling

During vascular development, wound repair, and inflammatory occlusive diseases such as atherosclerosis and post-angioplastic restenosis, VSMCs undergo rapid phenotypic switching from the "differentiated" or "contractile" state to the highly "migratory" and "proliferative" state, [12]. VSMCs switch from a "contractile" to a "synthetic" proliferative phenotype is regulated by a rise in $[Ca^{2+}]_i$, which activates Ca^{2+}-dependent factors of transcription [30]. Several TRPs seems implicated in $[Ca^{2+}]_i$ enhancement during VSMCs proliferation and vascular remodelling [12]. Studies from our laboratory showed that TRPC1 associates with Orai1 upon agonist stimulation and their protein levels were significantly increased in synthetic aortic VSMCs compared to quiescent cells [31]. We showed that the increase in SOCE in synthetic VSMCs was inhibited either by TRPC1 or Orai1 protein knockdown. We also demonstrated that protein knockdown of TRPC1 or Orai1 inhibited SOCE activation of transcription factor, P-CREB, and further VSMCs proliferation [31]. Kumar and colleagues also have shown that phenotypic switching of VSMCs caused an up-regulation of TRPC1 levels accompanied with enhanced Ca^{2+} entry and proliferation, and TRPC1 specific antibody blocked all these effects [32]. Others studies have shown that TRPC1 is up-regulated in proliferative human coronary VSMCs [33] and rat aorta [34]. Interestingly, TRPC3 and TRPC6 over-expression was observed in patients with idiopathic pulmonary arterial hypertension that is characterised by proliferation of pulmonary artery smooth muscle cells (PASMCs) [35]. Other studies demonstrated that TRPC6 is up-regulated in PASMCs treated with PDGF and ET-1 [15], meanwhile the TRPC3 blocker, Pyr3, inhibited VSMC proliferation and prevented stent-induced arterial remodelling [36], although it should be noted here that Pyr3 also might block Orai channels [37]. Furthermore, others TRPs such as TRPV1 and TRPV4 are up-regulated by hypoxia [38], and are involved in migration of PASMCs [39]. Beside, TRPM3 is expressed in both contractile and proliferative VSMCs [40], and Mg^{2+} influx through TRPM7 stimulated VSMCs growth and differentiation [41].

To summarize, evidences suggesting functional importance of TRPCs in the vasculature are considerable and TRPs role in vessel reactivity and especially in VSMCs proliferation make them an attractive potential targets for therapeutic strategies to improve vascular disorders and related pathologies [42].

2.2. Overview of the role of TRP channels in cardiac disorders

The heart is a pump that beats more than 100,000 times daily, due to an electrical conduction system, which connects the sinoatrial (SA) node to cardiac myocytes via specialized muscle fibres as the bundle of His, and the fibres of Purkinje. While TRPs physiological role still remains under debate, considerable advances have been made in determining their contribution to cardiomyopathies, cardiac fibrosis, cardiac remodelling, etc. [10,13,43]. In this review we will focus on the role of TRPs in cardiac hypertrophy and in cardiac conduction disorders.

2.2.1. Role in arrhythmogenesis

TRPM4 and several TRPCs are present in SA node cells and some of them are thought that interact with the $Ca_v1.2$ channel to regulate cardiac pacemaking, conduction, and ventricular contractility during cardiogenesis [44]. However, it is unclear whether any of these channels is involved in the cation conductance that regulates the pacemaker activity. Recently, the involvement of TRPM4 in cardiac conduction anomalies has been well documented [45]. Several TRPM4 mutations were detected in family with cardiac conduction disorders, including progressive familial heart block type I [46], isolated cardiac conduction diseases [47] and atrioventricular block and right bundle branch block in patients with Brugada syndrome [48]. Most of these mutations resulted in an increase of TRPM4 expression and in current density, which disturb apparently cardiac conduction by prolonging membrane depolarization. On the other hand, others TRPs seem involved in arrhythmia such as TRPM7 and TRPC3 that are significantly up-regulated in human atrial fibroblasts from patients with atrial fibrillation [49,50] and TRPC3 or TRPA1 which regulate heart rate [26].

2.2.2. Cardiac hypertrophy

Cardiac hypertrophy develops in response to increased pressure or mechanical overload due to cardiac diseases such as valvular stenosis or hypertension. Its well known that the calcineurin-NFAT complex is

one of the key mechanisms that switch on the genes that cause cardiac hypertrophy (see [51]); and a role for TRPC channels and the calcineurin-NFAT complex has been confirmed in several studies (as reviewed in [10,52,53]). Stimulation with agonists such as endothelin-1, phenylephrine and angiotensin that induce hypertrophy upregulated TRPC1 TRPC3, and TRPC7 [10]. In this way, TRPC1-deficient mice failed to develop cardiac hypertrophy in response to pressure overload and neuroendocrine stimulation [54]. Meanwhile, overexpression of TRPC3 in mouse cardiac myocytes promoted store-operated Ca^{2+} entry stimulation of calcineurin-NFAT signalling, which secondarily stimulated cardiac hypertrophy [55]. Another report has shown that TRPC6 are upregulated in failing human hearts and in also mouse hearts in response to activated calcineurin-NFAT pathway activated by pressure overload [56]. Conversely, TRPC6 knockdown prevented Angiotensin–II induced NFAT activation and hypertrophic responses in rat cardiomyocytes [57]. Interestingly, cardiac myocytes transfection with dominant negative constructs of TRPC3, TRPC6, or TRPC4, showed reduced hypertrophic responses induced either by neuroendocrine agonist infusion or pressure overload stimulation through calcineurin/NFAT activation [51,53]. Others TRPs such as TRPV1, TRPV2, PKD1 and PKD2 seem also involved in heart hypertrophy [10]. Indeed, TRPV1 knockdown protected mice heart from ischemic injury and also from pressure overload induced cardiac hypertrophy [58]. Furthermore, cardiac myocytes isolated form PKD2 null mice displayed a sever alteration in intracellular Ca^{2+} concentration handling, which has been also related to heart hypertrophy observed in patients with autosomal dominant polycystic kidney disease [59].

Taken together, several findings using different approaches in animal model suggest that TRPs, either TRPC1/3/4/6/7, TRPV1/2, or PKD1/2, are important mediators of pathological hypertrophy and may serve as potential therapeutic targets [9].

3. Involvement of TRP channels in the pathogenesis of diabetes mellitus

3.1. Expression and functional role of TRP channels in β-cells

The secretion of insulin by the pancreatic β cell is a complex process driven by changes in membrane potential and $[Ca^{2+}]_i$. Briefly, when glucose enters the β cell, via the GLUT-2 transporter, the metabolism of glucose produces ATP, which closes ATP-sensitive K^+ channels. Consequently, the membrane potential depolarizes, which, in turn, results in the activation of voltage-dependent Ca^{2+} channels. The subsequent rise in $[Ca^{2+}]_i$, together with the resulting Ca^{2+}-induced Ca^{2+} release, leads to the exocytosis of insulin-containing vesicles [60,61]. The model of glucose-induced insulin secretion is based on membrane depolarization upon closure of the ATP-dependent K^+ channels; however, this phenomenon requires the existence of an inward current that drives the membrane potential to more positive values. The nature of this background current, which might be due to Cl^- efflux or cation influx, remains unknown [62], but TRP channels have been presented as candidates for this depolarizing current [63,64].

A variety of TRP channels have been described both in primary β-cells or insulin-secreting cell lines, including TRPC1, TRPC2, TRPC3, TRPC4, TRPC5, TRPC6, TRPM2, TRPM3, TRPM4, TRPM5, TRPV1, TRPV2, TRPV4 and TRPA1 [63,65–67]. Most of these isoforms are expressed in insulinoma cell lines derived from mouse (MIN6 and βTC3) or rat (INS-1). But also many of them have also been described in primary tissue, including the expression of TRPC1, TRPC2, TRPC3, TRPV2, TRPV4, TRPM2 and TRPM3 reported in mouse islets, TRPC1, TRPC4, TRPM2 and TRPV1 in rat islets, and TRPM2, TRPM4 and TRPM5 expressed in human islets (for a review see [63,65]).

Despite several TRPC family members have been described in primary and culture insulin-secreting cells, the role of TRPC channels in insulin secretion remains uncertain. Early studies suggested that TRPC channels mediate the uncharacterized depolarizing current that account for the Ca^{2+}-release activated cation current in ETC3 cells [68]. The analysis of blood glucose concentration in TRPC4-deficient and wild type mice did not reveal differences at basal glucose levels under fasting conditions or following intraperitoneal glucose administration [69]. A more recent study has revealed that Ca^{2+} entry through TRPC4 channel activation is essential for leptin-induced AMPK activation, which in turn promotes ATP-sensitive K^+ channels trafficking to the plasma membrane, thus providing evidence for a role of TRPC4 in insulin release in rat INS-1 and primary pancreatic β-cells [70].

The role of TRPM channels has been more extensively investigated in insulin-secreting cells. Knock-out of TRPM5 has been reported to attenuate [71] or abolish [72] glucose-induced insulin release. The TRPM5-mediated current is of a small magnitude (~20 pA at -80 mV at maximal stimulation); therefore, this channel is able to influence electrical activity, regulating fast $[Ca^{2+}]_i$ oscillations, during glucose stimulation, when ATP-sensitive K^+ channels are closed and consequently there is a high electrical resistance [61,65,71]. Glucose has been reported to activate TRPM5 by different mechanisms that includes rises in $[Ca^{2+}]_i$ [73], changes in membrane potential [73] or cytosolic arachidonic acid concentration [74] and even as a result of the direct activation of the sweet taste receptors T1R2/T1R3, which have also been reported to be expressed in pancreatic β-cells [75]. TRPM5, in addition to TRPM4, have also been involved in the regulation of insulin release due to the actions of neurotransmitter, such as acetylcholine, during the cephalic and enteric phases of secretion, a mechanism involving a distinct $[Ca^{2+}]_i$ -insulin secretion coupling [72]. Nevertheless, the role of TRPM4 in insulin secretion evoked by glucose is uncertain. In insulin-secreting cell lines, such as INS-1, HIT-T15, RINm5F, β-TC3, MIN-6 and the α-cell line INR1G9 cells, inhibition of TRPM4 (i.e. by expressing a dominant negative TRPM4 construct) has been reported to attenuate glucose-induced both Ca^{2+} signals and insulin release, thus suggesting that Ca^{2+} entry through TRPM4 is an important component for Ca^{2+} signals and insulin release [76,77]. In addition, TRPM4-containing vesicles are translocated to the plasma membrane upon cellular stimulation, which might play a relevant role in the exocytotic mechanism [76,77]. However, studies on TRPM4-deficient mice reported similar tolerance to intraperitoneal injection of glucose thatn wild type animals and no difference in glucose-stimulated insulin secretion from freshly isolated pancreatic islets was detected [78]. These data indicate that TRPM4 might not be required for the signal mechanism following glucose stimulation.

TRPM2 has been described as a cation-permeable channel activated by H_2O_2 in the insulinoma cell line CRI-G1 [79]. In addition to its role in β-cell apoptosis, TRPM2 has been suggested to contribute to insulin secretion induced by glucose in siRNA TRPM2-treated mouse pancreatic islets [80] and TRPM2-deficient mice [81], due to a reduced increases in $[Ca^{2+}]_i$, thus suggesting that TRPM2 contributes to Ca^{2+} signals during glucose stimulation. In addition to the conduction of Ca^{2+} influx in β-cells, TRPM2 has also been found localized in the lysosomes and might be involved in lysosomal Ca^{2+} release, thus participating in multimodal signaling elements regulating Ca^{2+} mobilization in β-cells through membrane depolarization, Ca^{2+} influx, and release of Ca^{2+} from intracellular stores [82].

The role of TRPV channels in insulin secretion is uncertain. TRPV1 channels have been reported in some nerve fibers of mouse islets [83] but not in human islets [65]. TRPV2 has been found in mouse MIN6 en culture β-cells, where this channel is translocated from the cytoplasm to the plasma membrane in response to insulin. Insulin-induced translocation of TRPV2 to the plasma membrane has been reported to be stimulated by glucose as a positive feed-back mechanism [84]. Finally, TRPV4 has been described as a cationic channel activated by a diversity of physical stimuli, including volume changes, osmolality or stretch [85]. It has been hypothesized that volume changes in β-cells induced by glucose stimulation might induce the activation of TRPV4 channels in these cells, thus contributing to the $[Ca^{2+}]_i$ changes observed in response to hypotonicity and volume increase [86].

TRPA1 channels are expressed in rat pancreatic islets and RINm5F cells, where treatment with 4-hydroxy-2-nonenal, allylisothiocyanate, H_2O_2, methylglioxal and 15-deoxy-[increment]12,14-prostaglandin J2 result in a dose-dependent increase in $[Ca^{2+}]_i$ and insulin release [67,87], which suggests that TRPA1 might represent the link between inflammatory signals, oxidative metabolism and insulin secretion.

3.2. Overview of the involvement of TRP channels in the pathophysiology of type 2 diabetes mellitus

3.2.1. Role TRP channels in the pathogenesis of type 2 diabetes mellitus

Diabetes mellitus (DM) groups several metabolic chronic disorders characterized by hyperglycemia and abnormal carbohydrate, protein, and fat metabolism. It is caused by the absence of insulin secretion by the pancreatic β-cells, or due to defects in insulin uptake in the peripheral tissue. DM is broadly classified under two categories, which include type 1 and type 2 diabetes. Whereas, type 1 DM is caused by an autoimmune destruction of the β-cells leading to a lack of insulin production, type 2 DM occurs as a combination of reduced amount of insulin production from pancreatic β-cells and peripheral insulin resistance [88].

Although the analysis of the role of TRP channels in the pathogenesis of DM deserves further studies, the current data suggest a possible link between TRP and type 2 DM. Type 2 DM is a polygenic disease involving a genetically determined susceptibility to β-cells dysfunction. This susceptibility includes abnormalities in genes encoding ion channels or in those that regulate ion channel function, membrane targeting or expression, which might lead to impairment of the β-cell electrical changes and, consequently, reduced insulin secretion [61,89]. Since TRP channels have been suggested to play a role in the excitation-secretion coupling in β-cells, functional modifications of TRP channels might play a role in the pathophysiology of type 2 DM. In this regard, a study reported nine TRPM5 single nucleotide polymorphisms that might be associated with prediabetic phenotypes in subjects at increased risk for type 2 diabetes, including insulin insensitivity, hyperglycaemia and low glucagon-like peptide-1 levels during oral glucose tolerance test [90].

A more recent study has reported that TRPM8, expressed in primary sensory neurons innervating internal tissues, might act as a regulator of serum insulin. TRPM8-deficient mice respond normally to glucose administration but show increased rates of insulin clearance compared with wild-type animals and increased expression of insulin-degrading enzyme in the liver [91].

Babes et al. have revealed that the anti-diabetic drug glibenclamide is an activator of TRPA1 channels, providing evidence for some adverse effects observed in diabetic patients treated with this drug. This study also reports that both inhibition of ATP-sensitive K^+ channels and activation of TRPA1 might explain the initial exacerbation of hyperinsulinism in glibenclamide-treated type 2 diabetic patients and the progressive deterioration of β-cell function [92].

3.2.2. TRP channels in the complications associated to type 2 diabetes mellitus

3.2.2.1. Role of TRP channels in diabetic vasculopathy. Diabetes mellitus is associated to dysfunction of both vascular endothelial and smooth muscle cells, the latter involving impaired relaxation or enhanced contractile response to agonists, which contributes to vascular complications [93]. The involvement of TRP proteins in vascular dysfunction is controversial with studies providing opposite results depending on the cell type investigated. In the saphenous vein from type 2 diabetic patients, TRPC1 and TRPC6 protein expression is significantly decreased, although their mRNA levels remained unchanged [94]. In contrast, in the caudal artery smooth muscle cells from Goto-Kakizaki rats, a diabetic model that shows a significantly lower systolic blood pressure as compared to control Wistar rats, the expression of TRPC1, TRPC4 and TRPC6 is significantly increased [95].

TRPC proteins abnormalities have also been suggested to contribute to the endothelial dysfunction associated to diabetes mellitus. Bishara et al have demonstrated that TRPC1 is overexpressed in bovine aortic endothelial cells upon chronic exposure to high glucose concentration, which results in enhanced Ca^{2+} entry in these cells. Although the link between the enhanced Ca^{2+} entry and endothelial dysfunction has not been completely established, this study suggest a potential role of TRPC1 in this process [96].

3.2.2.2. Role of TRP channels in platelet hyperactivity associated to type 2 diabetes mellitus. While the pathophysiology of types 1 and 2 DM is different, most of the complications are similar, which may include macrovascular and microvascular complications. Platelets from type 2 diabetic patients exhibit enhanced activity, which contributes to the development of micro- and macroangiopathy [97,98]. Platelets from diabetic subjects show altered Ca^{2+} homeostasis, including reduced Ca^{2+} extrusion and enhanced Ca^{2+} release from intracellular stores and influx, leading to both increased resting $[Ca^{2+}]_i$ and response to agonists [99]. We have reported several differences in the expression of Ca^{2+}-permeable channels in platelets from diabetic donors as compared to healthy individuals, including enhanced expression of Orai1 and TRPC3, together with a reduced expression of TRPC6 in diabetic subjects [100]. Treatment of platelets from healthy humans with high glucose has been reported to increase surface expression of TRPC6 in a time- and concentration-dependent manner, and by a phosphatidylinositol 3-kinase-dependent pathway, which is accompanied by an increased non-capacitative Ca^{2+} entry [101]. Furthermore, platelets from diabetics patients show an enhanced endogenous production of reactive oxygen species, resulting in enhanced activity of the Bruton's tyrosine kinase or proteins of the Src family of kinases [102], which have been shown to be required for platelet Ca^{2+} entry and function [103,104]. The increased Ca^{2+} influx in response to agonists in platelets from type 2 diabetes has been attributed to different abnormalities. First of all, the Na^+/Ca^{2+} exchanger operates in reverse mode, thus introducing Ca^{2+} into the cell, which contributes to the enhanced Ca^{2+} entry observed in response to thrombin [105]. In addition, the non-capacitative Ca^{2+} entry pathway is increased in cells from diabetic subjects [106]. On the other hand, under conditions that avoid autocrine platelet activation and using Mn^{2+} as a surrogate for Ca^{2+} entry, to avoid interference with Ca^{2+} extrusion via active pumping by the PMCA or Na^+/Ca^{2+} exchange, we have found that in platelets from type 2 diabetics SOCE is selectively reduced, probably due to impairment of the association of TRPC1 and TRPC6 with STIM1 and Orai1 [106], two key components of SOCE in human platelets [107,108]. Nevertheless, even though SOCE is attenuated in these cells, the overall Ca^{2+} influx stimulated by agonists is significantly increase in platelets from type 2 diabetic patients, which contributes to platelet hyperaggregability and hyperactivity, which supports the role of TRPC proteins as potential therapeutic targets for the treatment of diabetic complications.

3.2.2.3. TRP channels in diabetic nephropathy. Diabetic nephropathy, a process characterized by nephrotic syndrome and diffuse glomerulosclerosis, is another diabetic complication caused by angiopathy of capillaries in the kidney glomeruli and one of the most prevalent disorders associated to TRP channel dysfunction. Both, TRPC1 and TRPC6 channels have been reported to play a relevant role in regulating glomerular filtration by modulating the contractile function of the glomerular mesangial cells; therefore, attenuation of the expression of these channels in mesangial cells might result in impairment of Ca^{2+} influx and consequently, abnormal glomerular hemodynamics in diabetic subjects [93]. Recent studies have demonstrated that TRPC1 expression is reduced in diabetic patients [94] and diabetic db/db mice [109]. Reduced TRPC1 expression has been found to occur in the later stages of diabetic nephropathy [109]. The attenuation of TRPC1 expression has been

attributed to impairment of the hepatic nuclear factor 4-alpha, which results in reduction of *trpc1* gene expression, which might, ultimately, result in the development of diabetes nephropathy [110]. More recently, the role of microRNAs (miRNA) in the development of diabetic complications has been investigated. MiRNAs are small non-coding RNAs that act by regulating the expression of their target genes. MiR-135a has been found to be upregulated in serum and renal tissue from patients with diabetic nephropathy, db/db mice, which has been associated with microalbuminuria and renal fibrosis. Upregulation of miR-135a attenuates the expression o TRPC1 and reduces SOCE during diabetic renal injury. Knockdown of miR-135a was found to restore the levels of TRPC1 and reduce the synthesis of fibronectin and collagen. The role of TRPC1 in this process has been further demonstrated by overexpression of this channel in mesangial cells, which was able to reverse the pathological effects of miR-135a [111].

Graham et al have reported that chronic high glucose exposure of glomerular mesangial cells and diabetes in streptozotocin-injected rats lead to downregulation of TRPC6 expression, which, in rats, occurs after 2 weeks of streptozotocin administration, thus suggesting a possible contribution of TRPC6 in the early stages of diabetes [112].

In human mesangial cells, downregulation of TRPC6 induced by chronic high glucose exposure has been attributed to enhancement of NADPH oxidase activity and/or expression level that increases endogenous reactive oxygen species, which, in turn, activate PKCα. Activation of PKCα downregulates either directly or indirectly TRPC6 expression in these cells [113]. Overproduction of reactive oxygen species is a characteristic pathological process in diabetes mellitus, that has also been observed in cultured cells chronically exposed to high glucose; therefore, oxidative stress has been suggested as a general mechanism for diabetes-associated TRPC protein dysregulation [93].

3.2.2.4. TRP channels in diabetes associated erectile dysfunction. Erectile dysfunction is a common alteration associated to diabetes whose pathogenesis might involve TRP channels. Analysis of the expression of different channels in the corpus smooth muscle cells from diabetic humans and rats revealed the presence of TRPC1, TRPC3, TRPC4 and TRPC6 with a higher expression level of TRPC4 in rats as compared to controls. Down-regulation of TRPC4 by *in vivo* gene transfer of dominant negative TRPC4 into the smooth muscle of the *corpus cavernosum* restored erectile function in streptozotozin-induced diabetic rats, and similar results were obtained by gene transfer of dominant negative TRPC6 [114], thus suggesting a relevant role for TRPC4 in the development of erectile dysfunction associated to diabetes mellitus [115].

Finally, several members of the TRPC, TRPM and TRPV subfamilies, as well as TRPA1 have been associated to the development of diabetic neuropathic pain as a result of dysregulation of intracellular Ca^{2+} homeostasis and the generation of reactive oxygen species [116,117].

4. TRP channels and tumorigenesis

TRP channels are known to respond to a diverse collection of chemical and physical stimuli, such as temperature or mechanical stress, reflected in their common presence in sensory neurons [118]. However, due to Ca^{2+} permeability of many of TRP channels, they often find themselves involved in the regulation of calcium homeostasis and the associated cellular processes [119]. TRP channels are known to play an influential role in the cell cycle, often by regulating gene transcription, as well as influencing other cellular processes such as proliferation, apoptosis or cellular motility [120]. Often, variations in expression of TRP channels are associated with changes in intracellular Ca^{2+} and alteration of proliferative pathways, promoting or inhibiting apoptosis in affected cells [119,121,122]. These properties of TRP channels naturally draw attention to them as to likely regulators of various mechanisms of cellular development.

4.1. Cancer and calcium homeostasis

Changes in the cell cycle that lead to cancer typically shift the balance towards enhanced proliferation, while simultaneously suppressing pathways leading to cell death [121]. Commonly, the disturbances in affected molecular pathways involve alterations in $[Ca^{2+}]_i$ homeostasis in cells. Pathways initiating apoptosis frequently involve alterations in calcium homeostasis through cytoplasmic, ER-mediated or mitochondrial mechanisms [123,124], while pro-proliferatory pathways often involve Ca^{2+} entry via the plasma membrane (PM) expressed ion channels [121,122,125]. On the other hand, the established tumor cell lines, as well as freshly transformed cells often lose sensitivity to calcium signals as well as the need for the external Ca^{2+} for proliferation and survival [126,127].

It should be noted that the observed patterns of intracellular calcium release suggest functional presence of ion channels not only in the PM, but also in a number of subcellular membranes, such as endoplasmic reticulum (ER), where they provide pathways for Ca^{2+} passage from various organelles [120]. The classical examples of such ion channels include the inositol 1,4,5-trisphosphate receptor and ryanodine receptor channels, that have been known for some time to be localized to the ER and to participate in regulation of apoptosis, [128,129]. However recent studies point at the intracellular localization of more and more ion channels [130] including first few examples belonging to the TRP superfamily, such as TRPM2, TRPM8 [131,132].

The principal Ca^{2+}-dependent pathways, affected by TRP channel activity and regulating the cell cycle, include pathways mediated by a calcium/calmodulin-dependent kinase II (CaMKII), which plays an important role in Ca^{2+}-calmodulin regulated calcium reuptake as well as T-cell selection and activation [133–135] and a nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a protein complex controlling transcription of DNA in response to various harmful stimuli [136,137]. Other important calcium-dependent factors regulating the cell cycle include calcium-dependent cysteine proteases, calpains and the calcium-dependent serine-threonine phosphatase calcineurin forming a combined calpain-calcineurin signalling complex [138] sensitive to local $[Ca^{2+}]$ and modulating the expression of interleukins which, in turn, stimulate cellular growth and differentiation [139]. Next, in this section, we discuss the involvement of the TRP channels in the tumorigenesis, grouping them by their principal effect on the progression on various types of cancer.

4.2. Influence of TRP

4.2.1. Pro-proliferative role of TRPs

The TRP channels known to enhance the proliferation of the transformed cells appear to be relatively uniformly distributed among the three subfamilies harboring the cell-fate affecting players: TRPC, TRPM and TRPV. We start our short overview with TRPV6, the ion channel playing principally pro-proliferative role and for which the most data has been accumulated.

Unlike the majority of the TRPV family proteins, which show clear voltage and temperature dependence and often serve as sensors in central and peripheral nervous systems [140], TRPV6 is not associated with known sensory function. The channel is known to have a Ca^{2+} selectivity greater than typical for TRPs; however it does not exhibit a typical single-channel behavior [141], which may explain the absence of the sensory function. Instead Ca^{2+} entry via this channel is modulated via changes to its expression induced by estrogen, progesterone, tamoxifen and vitamin D, affecting proliferation and survival of cancer cells [142,143]. The channel is known to be naturally present in the epithelial cells of kidney, intestine, placenta and pancreas, with its expression being elevated upon malignant transformation in carcinomas of colon, thyroid gland, ovary and breast as well as chronic myelogenous leukaemia cell [143–149]. The channel is also known to play an important role in the prostate cancer progression, with its very low expression levels in

normal tissue substantially increasing in transformed cells and during the development of metastases [145,148]. In these phases of cancer the TRPV6 expression was shown to be inhibited by dihydrotestosteron, - an androgen receptor agonist and stimulated by becalutamide, - an androgen receptor antagonist [145,146,150]. Interestingly, its translocation to the PM has been shown to be mediated by Orai1 - the ion channel responsible for SOCE [151].

Another member of the TRPV family, the TRPV2 channel has been shown to be important for the growth and invasive properties of prostate tumors [152] while its stimulation in glioblastoma cells made the malignant tissues more sensitive to cytotoxic chemotherapeutic agents [153]. A preliminary indication of possible expression level changes of TRPV5 together with TRPV6 was reported in non-small-cell lung cancer [154]; however further characterization is necessary to confirm this.

The studies of the TRPC family involvement in carcinogenesis have originally been concentrated on the TRPC1 channel, which has been implicated in regulation of cell fate and motility [155–158]. Interestingly, the role that TRPC1 plays was shown to be different, depending on the stage of cancer considered. While in normal tissues TRPC1 promoted cell proliferation, in tumour tissues the presence of protein tended to shift balance towards apoptosis [8]. The channel is also known to be implicated in the regulation of the motility of the nasopharyngeal carcinoma and cell lung carcinoma cells, human malignant gliomas [159–161]. These observations concentrating on the TRPC1 have recently been expanded by the observations that TRPC5 and 6 also play important roles in the advancement of carcinogenesis although in alternative ways, due to belonging to different TRPC subgroups and exerting differential effects on physiological factors [162]. Thus, TRPC6 modulates the progression of gastric cancer via regulation of G(2)/M phase transition [163], and is associated with proliferation of several types of cancer cells, including prostate cancer LNCaP [164] and human hepatoma cells [165], while TRPC5 is essential for induction of a P-glycoprotein pump, that is overproduced in cancer cells leading to a suppression of anticancer drug resistance [166].Furthermore, TRPC3 and, mainly, TRPC6 have been found to be overexpressed in breast cancer epithelial cells and breast cancer biopsy tissues [167,168]. In addition, TRPC6 is, with TRPC1, TRPM7, TRPM8, and TRPV6, among the channels overexpressed in human breast ductal adenocarcinoma. While TRPC1, TRPM7 and TRPM8 expression has been reported to correlate with proliferative parameters, TRPV6 has been found to be mainly overexpressed in the invasive breast cancer cells [169]. Altogether, these findings present TRP channels as candidate targets for breast cancer diagnosis and therapy.

Similarly to TRPC and TRPV subfamilies, the TRPM family contains multiple members having pro-proliferative effect in transformed cells, TRPM4, 5 and 7. Initial evidence of TRPM4 and TRPM5 involvement in cancer was limited to observations of alterations in their expression levels in CD5+ B-cell lymphomas and Wilms tumours and rhabdomyosarcomas (Beckwith-Wiedemann syndrome) respectively [170,171]. Later, changes in the expression level of TRPM4 were found to be important for the proliferation of the prostate cancer cells in the androgen-independent phase and cervical cancer-derived HeLa cells [172–174]. However the majority of evidence in the TRPM family concentrates on the TRPM7 channel, which is implicated in enhancing proliferative potential of the grade III breast tumour cells [175] as well as participating in gastric and pancreatic cancers [176–178], human hypopharyngeal squamous cell and nasopharyngeal carcinomas [179,180], prostate cancer [181] and enhances invasive properties of neuroblastoma [182–184].

4.2.2. Pro-apoptotic role of TRPs

Similarly to the TRP channels having a pro-proliferative effect on transformed cells, the pro-apoptotic players are uniformly distributed among the TRP subfamilies. The TRPC and TRPV subfamilies are represented by only one channel each: TRPC3 and TRPV1, and TRPM1 and 2 represent the TRPM subfamily. Starting with the TRPC3 channel, its expression was shown to be elevated by a prolonged Ca^{2+} store depletion, affecting alpha-adrenergic stimulation and anti-apoptotic signaling in various prostate cancer cells [185,186]. Stimulation of its expression or activity was also shown to enhance apoptosis in rat cardiomyocytes or to attenuate tumor proliferation and migration in MCF-7 breast cancer cells [187]. Interestingly, in ovarian cancer cells activation of TRPC3 actually enhances cell proliferation and contributes to this type of cancer [188]. The second single protein subfamily representative, the TRPV1 channel, is shown to change its expression levels during the tumorigenesis in prostate, colon, bladder and pancreas cancers [189–192]. The channel is known to induce apoptosis following its stimulation by vanilloids in prostate and colorectal cancers [193,194].

Talking about the first representative of the TRPM subfamily, the TRPM1 channel, it is necessary to note that, similarly to TRPV6, the channel does not exhibit a common single-channel type of gating and instead is considered to be a leak channel modulated by Go protein in response to activation of the mGluR6 receptor, which brings about a complete closure of the channel [195,196]. Similarly to TRPC1, TRPM1 channel exhibits a complex pattern of expression that depends on the stage of the cancer. It is found in human melanoma cells at high levels in benign tissues with its levels decreasing in primary melanomas and no appreciable amounts in metastatic tissues [190,197,198]. These changes in the expression levels are reportedly controlled by microphthalmia transcription factor in a way dependent on the state of cellular differentiation [199,200] and these changes in the level of TRPM1 expression are suggested to control apoptosis induction at different stages of cancer [197,201]. Interestingly, the microRNA miR-211 that is localized to intron 6 of the *Trpm1* gene shows the same pattern of expression and was recently shown to affect epithelial ovarian cancer as well as melanoma by arresting cells in the G0/G1-phase, inhibit proliferation and induce apoptosis [202,203]. Additionally, a short isoform of the chanel (TRPM1-S) is known to exist and control the trafficking of the full-length TRPM1 to the plasma membrane [204,205].

The second member of the TRPM family covered in this subsection is the TRPM2 channel, known to react to TNF-α or oxidative stress with its activation leading to decreased viability and increased apoptosis of the immune cells [206]. Additionally its overexpression or increased activity and the associated increases in Ca^{2+} influx have been shown to contribute to apoptosis induction in rat insulinoma RIN-5 F and in U937 monocyte cells, and lysosomal calcium release was shown to contribute to apoptosis induction in the rat β pancreatic cell line INS-1 [82,207]. Similarly, inhibition of histone deacetylase upregulated TRPM2 and induced apoptosis in T24 bladder cancer cells[208]. Interestingly, in prostate, TRPM2 changes its localization from near-PM to nuclei with its knockdown inhibiting the growth of the cancerous but not that of the normal cells [131]. Similarly to TRPM1, TRPM2 has a short isoform that, when combined with the full length protein, exhibits a strong dominant-negative effect. Co-expression of this isoform in HEK293 cells overexpressing full length TRPM2 suppressed Ca^{2+} entry and protected cells from death, confirming the role of the channel in cell survival [209].

4.2.3. Migration

Many of the TRP channels that were already mentioned to play pro-proliferatory or pro-apoptotic roles have also been shown to affect the motility of the transformed cells. Thus, recent studies position TRPM7 as a part of mechanosensory complex driving metastasis formation and invasiveness of breast cancer cells, in a manner involving the kinase domain of the channel and phosphorylation of Src and MAPK but not AKT kinases [210–213]. In breast cancer cells expression of TRPM7 channel was shown to regulate EGF-induced STAT3 phosphorylation and expression of the marker of epithelial-mesenchymal transition vimentin [214].

Another member of the TRPM subfamily involved in the regulation of motility of the transformed cells is TRPM8 channel. It was initially found to be present at high levels in prostate tissues [215] with its expression levels varying during the progression of the prostate cancer following a complex pattern: increasing in the cancerous tissues, however

decreasing and disappearing in the advanced, metastatic phases of prostate cancer [216,217]. The channel has recently been shown to be involved in the regulation of motility and tumorigenesis of multiple cancer types, such as oral squamous carcinoma, pancreatic ductal adenocarcinoma cells and lung cancer [218–220]. In prostate cancer cells the modulatory effect of TRPM8 on motility of prostate tumors was known even longer, with recent reports starting to shed light on the specific mechanisms that implicate newly identified TRP channel-associated factors (TCAFs) as proteins regulating TRPM8 activity and its trafficking to plasma membrane [221,222].

The TRPV2 channel was also shown to stimulate migration of the PC3 prostate cancer cells while being activated by endogenous lysophospholipids [223]. On the pro-apoptotic side, the principal evidence elucidating role of the involved channels in regulating cellular motility lies primarily with the presence of TRPM1 negatively correlating with metastasis formation [197,201]. These observations, while still scarce, seems to point at a universal pattern of pro-proliferatory channels also having a stimulatory effect on cell motility, and pro-apoptotic players having a tendency to inhibit motility.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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