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REVIEW

Dynamics and physiological meaning of complexes between ion channels and integrin receptors: the case of Kv11.1

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Abstract

The cellular functions are regulated by a complex interplay of diffuse and local signals. Studying the latter is challenging, but experimental work in cell physiology has led to recognize that understanding a cell's dynamics requires a deep comprehension of local fluctuations of cytosolic regulators. Macromolecular complexes are major determinants of local signaling. Multienzyme assemblies limit the diffusion restriction to reaction kinetics by direct exchange of metabolites. Likewise, close coupling of ion channels and transporters modulates the ion concentration around a channel mouth or transporter binding site. Extreme signal locality is brought about by conformational coupling between membrane proteins, as is typical of mechanotransduction. A paradigmatic case is integrin-mediated cell adhesion. Sensing the extracellular microenvironment and providing an appropriate response are essential in growth and development and have innumerable pathological implications. The process involves bidirectional signal transduction by complex supramolecular structures that link integrin receptors to ion channels and transporters, growth factor receptors, cytoskeletal elements, and other regulatory elements. The dynamics of such complexes are only beginning to be understood. A thoroughly studied example is the association between integrin receptors and the voltage-gated K^+ channels Kv11.1. These channels are widely expressed in early embryos, where their physiological roles are poorly understood and apparently different from the shaping of action potential firing in the adult. Hints about these roles come from studies in cancer cells, where Kv11.1 is often overexpressed and appears to reassume functions it presumably exerts during embryogenesis, such as controlling cell proliferation/differentiation, apoptosis, and migration. Kv11.1 is implicated in these processes through its linking to integrin subunits, which in turn regulates channel expression. Specific cellular functions, such as proliferation and migration, appear to be modulated by distinct conformational states of the channel (e.g., open and closed), whose balance is affected by the link with integrin subunits.

cancer; cell adhesion; conformational states; development; ERG

INTRODUCTION: LOCAL AND DIFFUSE CELL SIGNALS

No matter how biophysically sophisticated we may be, when reasoning about cell signaling it is difficult to resist the temptation to view the cell as a small sac containing an electrolytic solution governed by the macroscopic physicochemical parameters. This intuitive analogy is acceptable under some respects but can otherwise lead us far astray. True, classic work has shown that the diffusion coefficient and mobility of K^+ in the axoplasm are close to those measured in aqueous solutions of similar ionic strength, suggesting that classic electrodiffusion can be applied in this context (1). Likewise, second messengers such as cAMP and inositol 1,4,5 trisphosphate (IP_3; 2, 3) can quickly coordinate by diffusion the activity of different parts of the cell (e.g., the apical and basolateral membrane of epithelia). Nevertheless, this simple line of reasoning cannot even be applied to all the physiologically relevant ions. As is well known, Ca^{2+} diffusion in the cytoplasm is considerably restricted by organelle absorption and protein binding (2, 4, 5), which reminds us that we cannot disregard the microscopic structure of cytosolic and membrane-associated cell compartments. There is however much more than this. Work of the last three decades has revealed the great physiological relevance of supramolecular complexes, which carry out cellular processes whose dynamics depend on closely interacting molecular components and cannot be understood by relying on macroscopic measurements, such as the determination of average cytosolic pH or $[Ca^{2+}]$. Mitochondrial physiology provides a major example. The random diffusion model of electron transfer along the inner mitochondrial membrane has been progressively substituted by a model in which the elements of large multiprotein aggregates undergo direct electron exchange, which is coupled to proton flux (6).

Recent work has considerably extended the spectrum of cell functions regulated by the proximity of

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molecular elements. In the extreme case, this entails direct conformational coupling (Fig. 1), which was to the best of our knowledge first proposed to mediate the excitation-contraction coupling in the T-tubules of skeletal muscle (7, 8).

A good example is offered by H^+ transport. The type I Na^+/H^+ exchanger (NHE1) is a large membrane protein with 13 transmembrane domains and a large cytoplasmic C-terminal domain, which closely interacts with the cytoskeleton, calcium-regulated proteins, and a variety of other regulatory elements (9). NHE1 phosphorylation stimulates the binding of carbonic anhydrase type II (CA-II) to the cytosolic face of the transporter, which tightly couples the H^+ generated from CA-II activity with the proton transfer domain of NHE1 (10). Other well-defined examples regard calcium signals. Store-operated calcium entry (SOCE) is a response to calcium depletion in intracellular stores. It is typically mediated by the Orai1 calcium channels expressed on the plasma membrane. These channels are activated through conformational coupling by stromal interaction molecule (STIM)1 proteins, which serve as calcium sensors on the endoplasmic reticulum (ER) membrane. When $[Ca^{2+}]$ in ER decreases, STIM1 proteins undergo a wide conformational change that leads to protein clustering and translocation to the ER-plasma membrane contact sites, through which STIM1 proteins can bind and activate Orai1 channels (11, 12). Moreover, the association of big conductance Ca^{2+}-activated K^+ channels (BK_{Ca}) and voltage-gated Ca^{2+} channels (Cav) is thought to permit quick localized Ca^{2+}-dependent regulation of K^+ channels during action potential (AP) repolarization (13).

Importantly, paradoxes may arise when neglecting the small scale of cellular compartments. In synaptic vesicles, a transmembrane electrochemical gradient established by H^+-ATPases favors neurotransmitter accumulation (14, 15). Measurements carried out by pH-sensitive fluorescent probes suggest intravesicle pH between 5 and 6 (16). It has been noted that as the volume of synaptic vesicles is $\sim 2 \times 10^{-20}$ L, with a pH $\sim$ 5, no more than 0.1 proton is present in each vesicle at a given time, on average (17). Once more, the macroscopic notion of concentration becomes meaningless, at this size scale. To gain a better picture of the trans-vesicle transport mechanism one should *1*) estimate the local $[H^+]$ close to the transporters' binding sites and *2*) consider the possibility of direct proton exchange between the pump and the antiporter. Solving the difficult experimental task of determining the local concentration fluctuations in subcompartments has driven some major lines of cell physiological research in the last three decades. A thorough understanding of local signaling could also help to explain how cells expressing a wide spectrum of different G protein-coupled receptors (GPCRs) could manage to obtain specificity of downstream responses, even though these depend on a limited number of signaling pathways. Indeed, recent results show that certain GPCRs can generate highly localized (approximately, about tens of nanometers) cAMP domains around the receptor itself, which appear to operate independently from similar domains generated by other GPCRs (18).

In the following, we expand on the implication of these concepts in the cellular response to the local extracellular environment, by focusing on recent advances in the comprehension of the mechanisms by which cells engage ion channels to transduce extracellular matrix (ECM) signals. In the final section, we compare in more detail the main features of local and diffuse signaling in different pathophysiological contexts. Broadly speaking, signal transduction between closely interacting molecules is quicker, more efficient, and decreases the signal-to-noise ratio. Second messenger cascades are more effective in carrying out slower large-scale coordination of cellular activity but can be energetically expensive, depending on the number of biochemical steps involved.

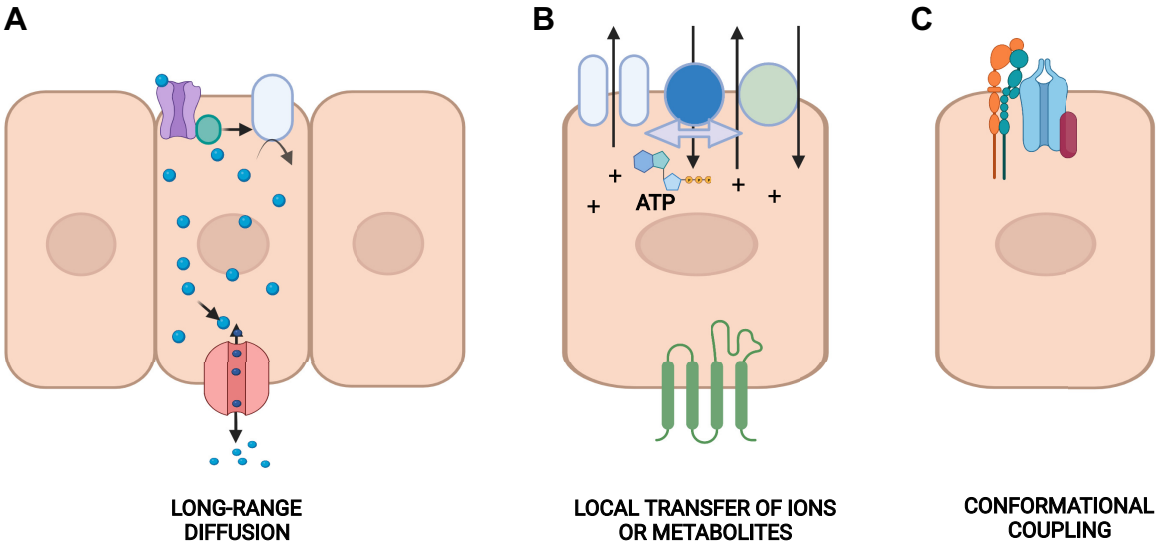

Figure 1. Long range and local signal transduction. *A*: long range diffusion; *B*: local transfer of ions and metabolites; *C*: conformational coupling. Created with BioRender.com.

INTEGRINS MEDIATE CELL INTERACTION WITH THE MICROENVIRONMENT BY MECHANOTRANSDUCTION AND DIFFUSE SIGNALS

Integrin receptors are heterodimeric integral membrane proteins formed by different pairs of α and β subunits with different affinities for ECM proteins such as collagens, fibronectin, laminin, and cell-cell adhesion receptors such as ICAM and VCAM (19). On binding its partner molecule, integrin activates by extending the extracellular domains of both subunits and separating their cytoplasmic tails. Activation stimulates integrin clustering and assembly of the focal adhesion complex, a large cytoplasmic signaling hub comprising hundreds of proteins, including integrin receptors and their interactors, proteins regulating the actin cytoskeleton, force transducers like talin and vinculin, and many other regulatory elements (20). Focal adhesion structures transmit to the ECM, the force generated by the cytoskeleton and in turn allow the cell to respond to the mechanical changes occurring in the matrix itself. Integrin activation thus mediates bidirectional signaling, and it increases ECM binding affinity while stimulating intracellular mechanisms that regulate cell motility and migration or differentiation (20).

Converting mechanical force into biochemical or electric signals is an essential step linking a cell with its environment during cell migration, morphogenesis, tissue differentiation and remodeling, and the related pathological aberrations, which occur e.g., in cancer, such as uncontrolled proliferation and metastasis. Integrins are essential players in these mechanisms, and thorough studies have clarified how the mechanical tension established across the plasma membrane leads to strengthen the interaction between extracellular ligands, integrin receptors, and the cytoskeleton (21). These studies also provide examples of the interplay between signal transfer by protein-protein interaction and signaling through ion-dependent and phosphorylation mechanisms. Studies on the force responses at levels ranging from the single-cell down to the single molecule are building a picture of the richness of these signaling mechanisms and how they can be integrated (21). By using a biomembrane force probe, Chen et al. (22) studied the conformational switches of single αLβ2 integrin on binding to ICAM-1. The initial weak bond is considerably strengthened and thus stabilized by the pulling forces, which also promote the recruitment of cytoskeletal proteins that strengthen the integrin-actin connection. Proposed mediators are talin, which binds directly to both the β-integrin cytoplasmic domain and to F-actin (23), and vinculin, whose integrin-binding sites are exposed by stretching and also binds F-actin (24). However, direct force application to β1 integrins can also induce a delayed conversion of unoccupied low-affinity integrins to the high-affinity state, which promotes cytoskeletal remodeling and thus reorientation, in capillary endothelial cells. In this case, the initial tension quickly (within seconds) activates stretch-activated Ca^{2+} influx through mechanosensitive transient receptor potential vanilloid 4 (TRPV4) channels leading to phosphatidylinositol 3-kinase (PI3K) activation (25), which recruits further integrins with a time course of minutes. Recent results also point to other types of stretch-activated ion channels as possible mediators of integrin-dependent signals. The newcomers in the field are the mechanosensitive PIEZO channels, which are generally permeable to cations (26). PIEZO1 has been detected in human gliomas, with expression correlating with tumor stage, and found to localize to focal adhesions (27). PIEZO1 appears to stimulate the β1 integrin-focal adhesion kinase (FAK) pathway, presumably through local Ca^{2+} influx. This regulates ECM remodeling, tissue stiffness, and proliferation, although the details of the interaction between PIEZO1 and β1 integrins remain to be dissected (27).

In summary, a cell is driven toward different destinies depending on local extracellular cues that include soluble and cell-bound ligands as well as insoluble ECM substrates. Integrin receptors are major players in the transduction process and appear to act by both protein-protein interaction, often entailing mechanotransduction, and signaling through ion fluxes and intracellular biochemical pathways (Fig. 2). These functions may be assisted by other membrane proteins that associate with integrins to form macromolecular complexes that constitute signaling platforms at the adhesive sites. Growing evidence points to ion channels as major interactors of integrin receptors.

MOLECULAR COMPLEXES BETWEEN INTEGRIN RECEPTORS AND ION CHANNELS: A HISTORICAL OUTLINE

The regulatory interaction between cell-cell or cell-substrate adhesion receptors and ion transport was first identified ~30 years ago. Evidence is now substantial for integrin-mediated adhesion (28). Early studies on integrin modulation of ion fluxes were prompted by two lines of reasoning. First, cell adhesion to the substrate controls cell motility and contraction through the actomyosin complex, which has long been known to be modulated by cytosolic calcium (29). Thus, integrin-dependent adhesion was found to stimulate calcium signals in migrating endothelia (30, 31), contracting smooth muscle (22), and stretching fibroblasts (32). Second, the transition between proliferation and differentiation was being increasingly recognized to be regulated by transmembrane ion flow, with early evidence, especially regarding Ca^{2+}, K^+ (33), and H^+ (34). In fact, integrin-dependent stimulation of K^+ currents favors the differentiation of leukemia cells (35, 36) and neurite extension in neuroblastoma (37). Moreover, cell spreading onto fibronectin was soon found to stimulate intracellular pH (pH_i) alkalinization in fibroblasts (38) and neutrophils (39). The underlying mechanisms turned out to be complex, as many parallel signaling pathways appear to be involved, which depend on cell type. Broadly speaking, initial work showed that the channel targets of integrin-mediated adhesion were regulated by classic intracellular pathways leading to phosphorylation/second messenger cascades (28, 40, 41). However, further work soon revealed that direct physical interaction also takes place between integrin subunits and voltage-gated (42–45) as well as ligand-gated (46, 47) ion channels. Evidence is now relatively abundant for voltage-gated potassium channels (Kvs). The complex between β1 integrin subunits and Kv11.1 channels [encoded by the human *ether-á-go-go*-related gene

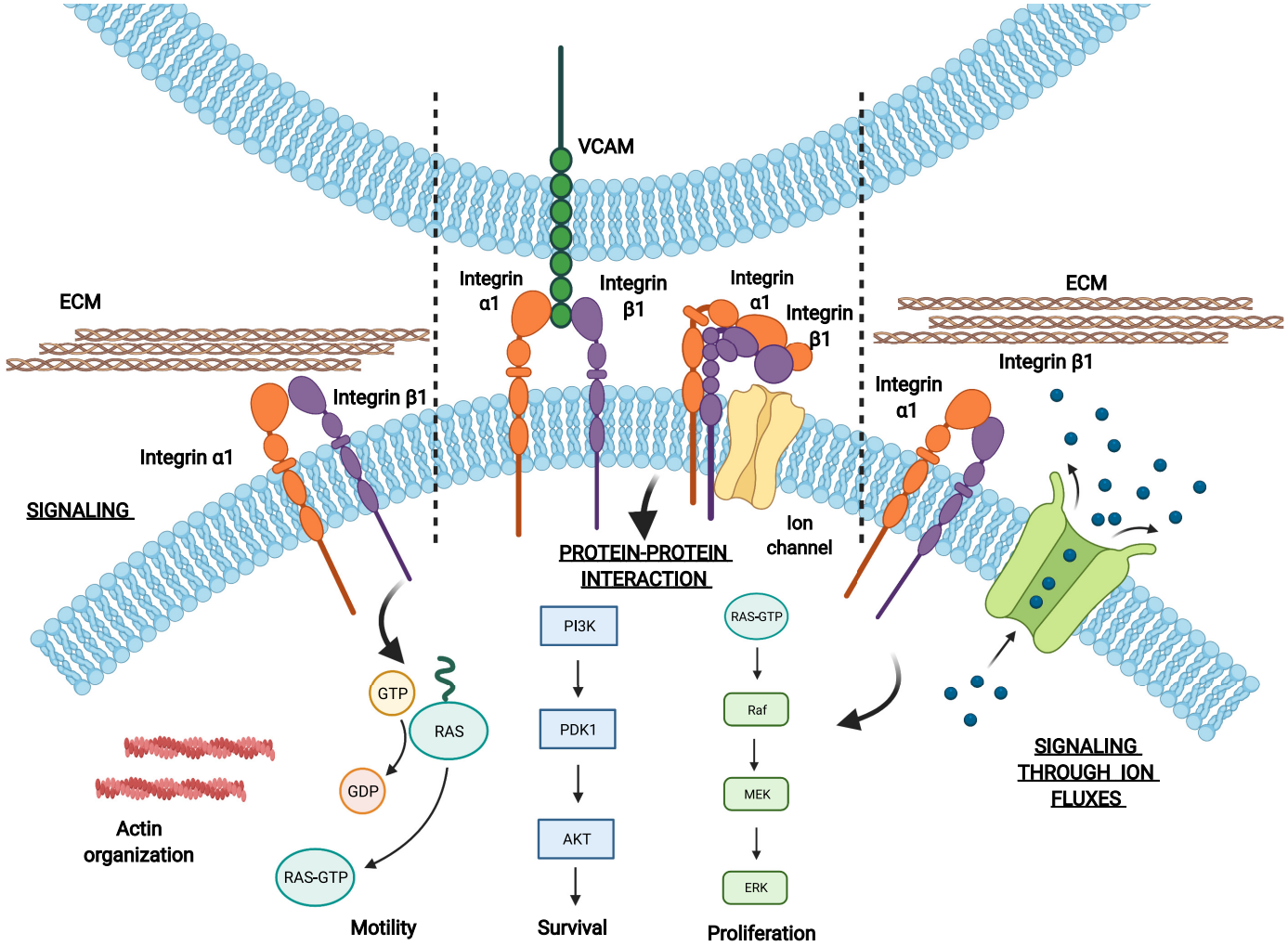

Figure 2. Integrin receptors main transduction processes. Integrin receptors are major players in the transduction process and appear to act as regulating signaling, protein-protein interaction, through mechanotransduction, but also mediating signaling via ion fluxes and intracellular biochemical pathways. Created with BioRender.com. ECM, extracellular matrix.

(*hERG1*) or potassium voltage-gated channel subfamily H member 2 (*KCNH2*)] is part of a supramolecular signaling hub comprising growth factor receptors, cytoskeletal elements, and other signaling proteins (48, 49), which will be fully described THE CASE OF KV11.1. In the brain, binding of Kv2.1 (encoded by *KCNB1*) to α5 integrins regulates cell plasticity and apoptosis (50, 51). Moreover, in an inflammatory context, β1 integrin-mediated binding of T helper 17 (Th17) cells to neurons that upregulate VCAM-1 stimulates glutamate release from Th17 cells themselves, leading to neuronal damage (52). The effect, which appears to be stronger in patients with multiple sclerosis, depends on SNARE (SNAP receptor protein) complex-dependent vesicle release stimulated by β1 integrin/Kv1.3 signaling (52). Although the molecular details await full elucidation, it is tempting to interpret these results in the light of previous observations showing direct coupling between Kv1.3 and β1-integrins (42, 45).

An independent line of research was prompted by the early observation that the ECM protein agrin stimulates postsynaptic clustering of nicotinic ACh receptors at the neuromuscular junction (NMJ; 53), which involves integrin receptors expressed on the postsynaptic membrane (54). Whether agrin exerts an inductive or stabilizing role (or both) in NMJ formation remains an open question (55). Nonetheless, subsequent work has shown direct interaction between presynaptic Cav and laminin in NMJ (56), and subsequent studies showed the complex to recruit α3-integrins, cytoskeletal elements, and active zone components in *Torpedo* electric organ synapses, similar to the NMJ (57). The studies on the ECM-dependent modulation of synaptic structures have been subsequently extended to the central synapses (47, 58–60). The role of integrin receptors in synaptic development and plasticity is beyond our scopes and we refer the reader to recent reviews (61, 62).

THE CASE OF KV11.1

Different Physiological Roles in Mature And Developing Excitable Tissue

Among the ion channel interactors of integrin receptors, the widest experimental evidence concerns Kv11.1, whose

interplay with integrins appears to be specific of developing and cancer tissues. Because of its peculiar voltage-dependent gating properties, Kv11.1 has distinct physiological roles in adult and developing organs. At depolarized (or positive) V_m, K_V11.1 activates and quickly inactivates, thus giving a little contribution to the overall K^+ conductance. On repolarization, however, inactivation is quickly removed and the channel thus contributes a significant transient K^+ current, which further accelerates and sustains repolarization. Next, the channel deactivates (and then closes), with relatively slow time constants (in the order of hundreds of millisecond; 63). These biophysical features make Kv11.1 an effective regulator of action potential (AP) shape and frequency, in mature excitable cells. In the heart, in particular, Kv11.1 underlies the cardiac repolarizing current rapid depolarizing current (IK_r). The mutant *hERG1* genes that lead to abnormally long repolarization (which is reflected in a longer electrocardiographic Q-T interval) are linked to the long QT type 2 (LQT2) syndrome, which can cause fatal arrhythmia (64, 65). In endocrine cells, Kv11.1 contributes to regulate hormone release, which is driven by action potential frequency (66, 67); in the central nervous system (CNS), it regulates neuronal spike frequency adaptation (68) and other aspects of excitability (reviewed in Ref. 69); in smooth muscle, it contributes to regulate contractility (70). Work in cardiac cells (71) and endocrine tissue (72) suggests that a macromolecular complex between Kv11.1 and integrin subunits is generally absent in mature excitable tissues. We attribute this fact to the prevalent association of Kv11.1, in mature tissues, with its canonical accessory subunits potassium voltage-gated channel subfamily E regulatory subunit 1 (KCNE1) and KCNE2. Direct experimental evidence is currently available for KCNE1, which indeed prevents the channel from associating with integrin subunits (71).

The other side of Kv11.1's function regards developing excitable tissues, before AP maturation, and cancer. In these tissues, K_V11.1 regulates the resting V_m, because of its steady-state properties. The K_V11.1 activation and inactivation curves cross around −40 mV. Hence, the K_V11.1 "window" current is centered around the typical resting membrane potential (V_{rest}) of cycling and tumor cells. In mouse development, the Kv11.1 transcript (*erg*) is first expressed in the heart and CNS at embryonic *day 9.5* (E9.5; 73, 74). Next, at midgestation (around E14), it also appears in peripheral ganglia (dorsal root ganglia, DRG; sympathetic ganglia, SG; and myenteric plexus), in the neural layer of retina, skeletal muscle, and other tissues (74, 75). In adult mouse and rat, Kv11.1 expression is maintained in the heart, various CNS structures, DRG, and retina (73, 74, 76–78), although with a more restricted pattern of expression. The function of Kv11.1 at early developmental stages is largely unknown. Because of the pathological implications in LQT2, several studies have investigated the results of impairing Kv11.1 in murine embryos. Kv11.1 loss-of-function leads to cardiovascular teratogenesis and embryonic lethality, likely caused by the severe alteration of cardiac rhythm and the associated propulsive flow (79). The defects in vasculogenesis, however, are independent of electrophysiological alterations and appear instead to depend on differentiative and proliferative signals downstream to the transforming growth factor β (80). This observation points to alternative early functions of Kv11.1, i.e., preceding the electrophysiological maturation. Further hints about these functions come from studies in quail embryos, where Kv11.1 is expressed in the heart at ∼E1.5 (stage 11, according to Hamilton and Hamburger, HH), and in CNS and eye at HH stage-13 (81). In situ hybridization on sections from older embryos (E3) detected expression in both cardiac atrium and ventricle, in the neural tube and encephalic vesicles, and in the myotome. At E4, the gene was expressed in the ciliary ganglion (CG) and the nervous part of the retina. Since E5, *erg* was also detected in DRG, SG, and adrenal gland (AG). CG, DRG, SG, and AG derive from the neural crest and were also investigated from an electrophysiological standpoint. In brief, neural crest cells explanted at the 10–13-somite stage (HH 10–11) display Kv11.1 currents, which are also observed during early differentiation of CG, DRG, SG, and AG. However, in these structures, Kv11.1 is progressively substituted by classic inward rectifier K^+ channels (IRK) during the electrophysiological differentiation process, which is characterized by a significant V_{rest} hyperpolarization (which would be not allowed by the steady-state properties of K_V11.1), and the appearance of the AP machinery (e.g., voltage-gated Na^+ currents). The timing of such a switch cover stages between E4 and E12 depending on the anatomical structure (82). In conclusion, Kv11.1 appears to exert peculiar physiological roles in early phases of mammalian and avian development. These roles are apparently different from those typically observed in adult organs, where Kv11.1 (when present) is mainly implicated in modulating action potential shape and firing. These early roles are still virtually unknown, especially as far as the interaction with integrin receptor is concerned. It is nonetheless intriguing to notice that the sequential pattern of expression of Kv11.1 and IRK revealed in peripheral nervous tissue is reversed in glioma tumors. The typical IRK (specifically, Kir4.1) expression in astrocytes tends to subside with glioma progression (83) and leaves the stage to other K^+ channels, including Kv11.1 (84) and the biophysically analogous Kv11.2 (85). In fact, a wealth of suggestions about the possible roles of Kv11.1 and the macromolecular complexes it forms with integrins before the establishment of excitability are provided by the biology of tumors.

Kv11.1 in Cancer

Kv11.1 is commonly overexpressed in human cancers and, what is more, it is functionally implicated in all stages of tumorigenesis, from cell proliferation and survival to the modulation of growth factor release, invasiveness, and metastasis (49, 86–92; references in Table 1). Therefore, Kv 11.1 represents a promising cancer biomarker. Because those processes where Kv11.1 is implicated are generally regulated by cell adhesion to the ECM, a unifying mechanism in the Kv11.1 role in neoplastic progression may indeed be constituted by the channel/integrin functional and physical link. Depending on the pathophysiological context, such interplay between the channel and the integrin can modulate different cancer-related signaling pathways. Especially common among these appear to be FAK, ERK, and AKT phosphorylation, nuclear factor kappa-light-chain-enhancer of activated B cells (NFkB), and hypoxia-inducible factor (HIF)-α activation and nuclear translocation, activation

Table 1. *Expression of Kv11.1 in cancer*

	Preclinical Data			Clinical Data			
Tumor Type	**Effects in vitro**	**Signaling pathway affected**	**Consequences of hERG1 or hERG1/β1 blockade in vivo**	**Expression data: % of patients**	**Clinicopathological correlations**	**Effects on survival (HR)**	**Refs.**
Head & Neck (HNSCC) Oral squamous cell carcinoma (OSCC)	HNSCC: Migration OSCC: Invasiveness	Sphingosine 1-phosphate (S1P) receptors	NA	HNSCC: 90% OSCC: 47%	HNSCC: Lymph node involvement advanced stage tumor recurrence, distant metastasis. OSCC: TNM stage, tumor differentiation, recurrence	OSCC: Reduced survival (univariate analysis)	93, 94
Glioblastoma Multiforme (GBM)	Proliferation, Ki67	Vegf	NA	GBM: 61.2% low expression, 38.8% high expression	VEGF	Independent negative prognostic factor (HR 1.536) Non torsadogenic hERG1 blockers improve survival	84
Neuroblastoma	Cell cycle regulation	NA	Reduction of mean tumor weight in mice treated with hERG1 and hERG1b inhibitor ZC88	NA	NA	NA	95
Lung cancer	Proliferation [Small cell lung cancer (SCLC)]	NA	NA	NA	NA	NA	96
Pancreatic cancer (Pancreatic ductal adenocarcinoma, PDAC)	ProliferationMigration invasiveness	EGF-R signaling pathway	Block of local growth and of metastatic spread	60% (TNM I–III)	GradingKi67EGF-R	Independent negative prognostic factor in TNM stages I–III (HR 2.12) (multivariate analysis)	97
Colorectal cancer	Invasiveness angiogenesisMetastasis	Akt, NFkB, HIF-1/2α, VEGF HIF-1/2α	Block of local growth and of metastatic spread	TNM stages I–III: 24.7% TNM stage IV: 86.25%	VEGFCAIXGlut-1 (inverse) EGF-R	Identification of high risk group in TNM I–III (HR 2.15) Positive factor for response to Bevacizumab in TNM IV (HR 0.30)	98–101
Barrett's esophagus (BE), esophageal adenocarcinoma (EA), esophageal squamous carcinoma (ESC)	NA	NA	NA	BE: 48%Dysplasia: 87.5% EA: 96%ESC	NA	Identification of patients with BE at high risk of adenocarcinoma progression (OR = 3.70)	102
Gastric cancer	Cell proliferationApoptosisVEGF-A secretion	AKT, pAKT, HIF2α, VEGF	Block of local growthCombined activity of hERG1 blockers and anti-VEGF-A antibodies (Bevacizumab)	TNM stages I-IV: 69%	Lauren's intestinal typeFundus localizationGrading (G1–G2)VEGF-A expression. TNM I and IIExpression in precancerous lesions	Negative prognostic factor in early stage (T1) patients (univariate analysis)	92,103–105
Pancreatic cancer (Neuro endocrine tumor, NET)	NA	NA	NA	TNM stages II-IV: 66%	Correlation with Ki67	Independent positive prognostic factor (HR 0.19) (multivariate analysis)	106, 107
Breast cancer	Induction of cell senescenceActivation of p21/waf transcriptionMetastasis	Ras-dependentDNA damageActin assembly	Block of metastatic spread	High expression(100% Luminal A) (70% Luminal B)(50% HER2 positive)(20% triple negative)	Molecular subtypeKi 67	High hERG1 patients have a longer PFS	71, 108
Endometrial cancer	NA	NA	NA	Hyperplasia: 0%Stage I–II EC :83%	NA	NA	109
Ovarian cancer	Proliferation	NA	NA	OC: 53.9% low expression, 20.2% high expression.	Epigenetic silencing through methylation in clear-cell tumors	Methylation status as potential prognostic marker	110–112

Continued

Table 1.— *Continued*

Tumor Type	Preclinical Data			Clinical Data			Refs.
	Effects in vitro	Signaling pathway affected	Consequences of hERG1 or hERG1/β1 blockade in vivo	Expression data: % of patients	Clinicopathological correlations	Effects on survival (HR)	
Melanoma	ProliferationMigration	MAP kinase/c-fos pathway.	NA	Thickness >4 mm and metastatic melanoma = very high expressionThin melanomas and benign melanocytic lesions = low expression	NA	NA	113
Osteosarcoma	Proliferation, migration, apoptosis	PI3K/Akt/NFkB	NA	Dysplasia: 0%OS: 72.72%	NA	NA	114

hERG1: human ether-á-go-go-related gene 1; HIF, hypoxia-inducible factor; HR, heart rate; NA, not applicable; NFkB, nuclear factor kappa-light-chain-enhancer of activated B cells.

of small GTPases and the modulation of f-actin organization and dynamics (Fig. 3 and Table 1).

Studying the dynamics of Kv11.1 interplay with the β1 integrin subunit has greatly contributed to uncover the oncological relevance of Kv11.1 overexpression. In tumor cells, the Kv11.1-mediated current increases when β1 integrin is activated by cell adhesion onto the ECM or by specific antibodies (37, 43, 115). The underlying mechanism is still uncertain, especially regarding the relative contribution of Kv11.1 activation and higher membrane expression. The implication of a G_i protein downstream to integrin engagement is suggestive of an increased channel transfer onto the plasma membrane (116). Regardless of the mechanism of channel stimulation, a complex regulatory interplay appears to occur between K_V11.1 and integrin subunits, which comprises different phases subsequent to cell adhesion. First, integrin-dependent Kv11.1 stimulation determines V_{rest} hyperpolarization. Such an early increase of the Kv11.1 conductive function appears to specifically regulate FAK phosphorylation and cell proliferation (71). Next, Kv11.1 physically associates with the β1 integrin subunit (37, 43, 87), which preferentially recruits Kv11.1 in the closed state (71, 117). Hence, formation of the macromolecular complex is accompanied by a decay of the hyperpolarization signal. Moreover, other signaling elements are recruited by the multiprotein structure, which exerts their downstream effects when they are bound to the complex, suggesting signal transfer by conformational coupling (115). One such mechanism is operant in colorectal cancer (CRC) cells. On integrin-dependent CRC cell adhesion, the Kv11.1/β1 integrin complex recruits the PI3K p85 subunit, which stimulates AKT phosphorylation and thus regulates autophagy (117). Because p85 specifically binds to Kv11.1, we hypothesize that Kv11.1 could transduce by conformational coupling the integrin-dependent microenvironment signal. This would point to a nonconductive function of K_V11.1, related to cell adhesion but different from canonical mechanosensitivity (as Kv11.1 is not gated by membrane strain, to the best of our knowledge).

Further recent evidence better clarifies the main role of the Kv11.1/β1 integrin complex, which can recruit other ion channels and transporters and appears to be mostly implicated in controlling cell motility and migration. In CRC cells, the β1 integrin-mediated adhesion increases pH_i by activating NHE1. On cell adhesion, the transporter assembles with β1 integrin and Kv11.1 and the complex sustains CRC cell motility (86; Fig. 3). Another Kv11.1-centered mechanism sustains cell motility in pancreatic adenocarcinoma (PDAC) cells. In these cells, the channel sustains prometastatic signals through a reorganization of f-actin in stress fibers and a modulation of filopodia formation and dynamics, thanks to the interplay with small GTPases, which also involves the modulation of $[Ca^{2+}]_i$ (88; Fig. 3). In leukemia cells, Kv11.1 forms a complex with β1 and the chemokine receptor, CXC chemokine receptor-4 (CXCR4), which triggers the activation of both the ERK1/2 and PI3K/Akt prosurvival signaling pathways. At the same time, leukemia cells became markedly resistant to chemotherapy-induced apoptosis (118; Fig. 3). Finally, the Kv11.1/β1 integrin complex recruits CA-IX, in clear-cell renal carcinoma (ccRC) cells and primary cancer tissues (119). Interestingly, hERG1 and CAIX together represent biomarkers of ccRC progression (119). In the light of the

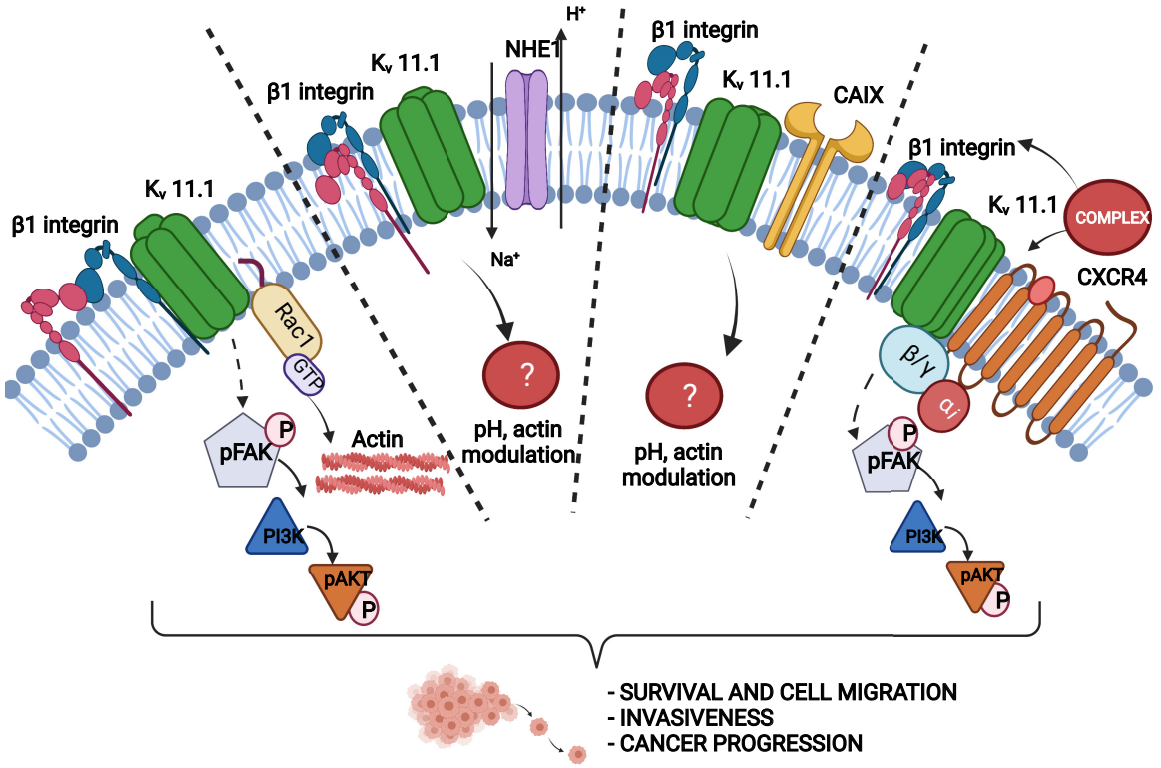

Figure 3. Integrin-mediated signaling in relation to Kv11.1. Different ion channel complexes mediate signaling transduction and regulate different aspect of cancer cell behavior, such as proliferation, survival, invasiveness, and progression. Created with BioRender.com. CXCR4, CXC chemokine receptor-4; NHE1, type I Na^+/H^+ exchanger.

available information on NHE1 and CAIX physiology, the Kv11.1/β1-integrin/NHE1 and Kv11.1/β1-integrin/CA-IX complexes constitute functional hubs that locally control intra- and extracellular pH, especially in hypoxic conditions, which drive progression-prone, prometastatic signaling pathways.

MACROMOLECULAR COMPLEXES IN THE PATHOPHYSIOLOGICAL CONTEXT

The features of local and diffuse signaling mechanisms are better appreciated in the context of sensory transduction, in which they have been thoroughly analyzed. Local signal transfer considerably accelerates the transduction process and decreases the effects of thermal noise by decreasing the diffusion distances (120). An extreme example is the conformational coupling between sensing structures and stretch-activated ion channels. This is typical of mechanoreceptors, where quickness of response is often essential. The underlying protein conformational changes can occur at time scales of microseconds and thus allow exquisite sensitivity to mechanical vibrations. In fact, the cutaneous Pacinian corpuscles are sensitive to mechanical vibrations in the order of 200 Hz (121), and auditory hair cells can discriminate sound frequencies up to ~20 kHz (122). In contrast, when the cellular signal must be transferred from the sensing region to distant compartments, such as synaptic terminals (as in photoreceptors) or the cell soma (as in olfactory receptors), a biochemical signaling cascade is needed, which is accompanied by an energy gain of ~5 orders of magnitude (122).

These considerations raise the question of whether the high speed and lower sensitivity to thermal noise provided by signal transfer through local signals and macromolecular complexes are at all necessary for the efficiency of the relatively slow cell adhesion processes that accompany embryonic development and pathological cancer cell spread. One possibility is that direct conformational coupling between integrins and ion channels avoids the energy expenditure generated by multistep biochemical cascades. An order of magnitude estimate is suggested by the simple case of a conformational transition between two protein states. The energy required for full state transition is in the order of 60 kJ/mol, which is approximately equivalent to the free energy released from cytoplasmic ATP hydrolysis (123). This suggest that activating, e.g., an ion channel by direct conformational coupling would require as much energy as a single step of a multistep signaling cascade leading to the same effect. Energy saving could be an advantage for the greedy embryonic cells, and even more for cancer cells. The latter could opportunistically select the most advantageous mechanisms normally used by the developmental process, as suggested by the widespread occurrence of Kv11.1/integrin interplay in tumors.

CONCLUSIONS AND PERSPECTIVES

The earlier-described mechanisms in cancer cell proliferation, survival, and migration clearly suggest potentially fruitful research lines aimed at clarifying the early roles of Kv11.1. Although these processes are aberrantly regulated in cancer,

and the occurrence of Kv11.1/integrin association in early development is presently speculative, a reasonable working hypothesis is that the morphogenetic functions of Kv11.1 should be related to the control of cell proliferation/differentiation and migration. Whether the frequent expression of Kv11.1 in cancer cells is a result of a selection process that leads the tumor to exploit some of the normal functions the channel exerts in development, or whether Kv11.1 is more suitable than other K^+ channels in undertaking some tumor-specific physiological roles remains to be determined. Considering the stringent energy requirements of cycling cancer cells, it is possible that exploiting an ion channel particularly susceptible to be recruited in macromolecular complexes and to carry out signal transfer by conformational coupling also offers energetic advantages. An energetic advantage could be also offered by the narrow steady state window current of Kv11.1, which rules out a strong K^+ flux in conditions in which V_{rest} oscillates slowly, as is typical of cancers.

From a pharmacologic standpoint, we notice that the multiprotein complexes described earlier offer unique opportunities for cancer cell targeting. The latter can be achieved by using several molecules such as bispecific antibodies, which are able to simultaneously bind two or more proteins, impairing the downstream signaling (115, 116, 124–126). In addition, the fact that Kv11.1 preferentially associates with integrin receptors in the closed conformation suggests that flexibility of treatment could be obtained by targeting different conformational states. Different cellular processes implicated in tumorigenesis can be targeted relatively independently, by adding or not open-channel blockers to the pharmacological toolkit. The comparative usefulness of selective as compared with combined treatment (to simultaneously target different conformational states) will have to be judged in specific pathological contexts.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.B., C.D., and A.A. drafted manuscript; A.B. and A.A. edited and revised manuscript; C.D. prepared figures; A.B., C.D. and A.A. approved final version of manuscript.

REFERENCES

1. **Hodgkin AL**, **Keynes RD.** The mobility and diffusion coefficient of potassium in giant axons from *Sepia*. *J Physiol* 119: 513–528, 1953. doi:10.1113/jphysiol.1953.sp004863.
2. **Allbritton NL**, **Meyer T**, **Stryer L.** Range of messenger action of calcium ion and inositol 1,4,5-trisphosphate. *Science* 258: 1812–1815, 1992. doi:10.1126/science.1465619.
3. **Kasai H**, **Petersen OH.** Spatial dynamics of second messengers: IP_3 and cAMP as long-range and associative messengers. *Trends Neurosci* 17: 95–101, 1994. doi:10.1016/0166-2236(94)90112-0.
4. **Hodgkin AL**, **Keynes RD.** Movement of labelled calcium in squid giant axons. *J Physiol* 138: 253–281, 1957. doi:10.1113/jphysiol.1957.sp005850.
5. **Zhou Z**, **Neher E.** Mobile and immobile calcium buffers in bovine adrenal chromaffin cells. *J Physiol* 469: 245–273, 1993. doi:10.1113/jphysiol.1993.sp019813.
6. **Sun F**, **Zhou Q**, **Pang X**, **Xu Y**, **Rao Z.** Revealing various coupling of electron transfer and proton pumping in mitochondrial respiratory chain. *Curr Opin Struct Biol* 23: 526–538, 2013. doi:10.1016/j.sbi.2013.06.013.
7. **Chandler WK**, **Rakowski RF**, **Schneider MF.** Effects of glycerol treatment and maintained depolarization on charge movement in skeletal muscle. *J Physiol* 180: 788–820, 1965. doi:10.1113/jphysiol.1976.sp011233.
8. **Gong D**, **Yan N**, **Ledford HA.** Structural basis for the modulation of ryanodine receptors. *Trends Biochem Sci* 46: 489–501, 2021. doi:10.1016/j.tibs.2020.11.009.
9. **Orlowski J**, **Grinstein S.** Na^+/H^+ exchangers. *Compr Physiol* 1: 2083–2100, 2011. doi:10.1002/cphy.c110020.
10. **Li X**, **Alvarez B**, **Casey JR**, **Reithmeier RA**, **Fliegel L.** Carbonic anhydrase binds to and enhances activity of the Na^+/H^+ exchanger. *J Biol Chem* 277: 36085–36091, 2002. doi:10.1074/jbc.M111952200.
11. **Prakriya M**, **Lewis RS.** Store-operated calcium channels. *Physiol Rev* 95: 1383–1436, 2015. doi:10.1152/physrev.00020.2014.
12. **Yu F**, **Machaca K.** The STIM1 phosphorylation saga. *Cell Calcium* 103: 102551, 2022. doi:10.1016/j.ceca.2022.102551.
13. **Berkefeld H**, **Sailer CA**, **Bildl W**, **Rohde V**, **Thumfart J**, **Eble S**, **Klugbauer N**, **Reisinger E**, **Bischofberger J**, **Oliver D**, **Knaus H**, **Schulte U**, **Fakler B.** BKCa-Cav channel complexes mediate rapid and localized Ca^{2+}-activated K^+ signaling. *Science* 314: 615–620, 2006. doi:10.1126/science.1132915.
14. **Farsi Z**, **Jahn R**, **Woehler A.** Proton electrochemical gradient: driving and regulating neurotransmitter uptake. *Bioessays* 39: 1600240, 2017. doi:10.1002/bies.201600240.
15. **Takamori S.** Presynaptic molecular determinants of quantal size. *Front Synaptic Neurosci* 8: 2, 2016. doi:10.3389/fnsyn.2016.00002.
16. **Beyenbach KW**, **Wieczorek H.** The V-type H^+ ATPase: molecular structure and function, physiological roles and regulation. *J Exp Biol* 209: 577–589, 2006. doi:10.1242/jeb.02014.
17. **Hassel B**, **Dingledine R.** Glutamate and glutamate receptors. In: *Basic Neurochemistry* (8th ed.), edited by Brady ST, Siegel GJ, Wayne Albers R, Price DL. Waltham, MA: Academic Press, 2012, p. 342–366.
18. **Anton SE**, **Kayser C**, **Maiellaro I**, **Nemec K**, **Möller J**, **Koschinski A**, **Zaccolo M**, **Annibale P**, **Falcke M**, **Lohse MJ**, **Bock A.** Receptor-associated independent nanodomains mediate spatiotemporal specificity of GPCR signaling. *Cell* 185: 1130–1142.e11, 2022. doi:10.1016/j.cell.2022.02.011.
19. **Shimaoka M**, **Takagi J**, **Springer TA.** Conformational regulation of integrin structure and function. *Annu Rev Biophys Biomol Struct* 31: 485–516, 2002. doi:10.1146/annurev.biophys.31.101101.140922.
20. **Doyle AD**, **Nazari SS**, **Yamada KM.** Cell-extracellular matrix dynamics. *Phys Biol* 19: 021002, 2022. doi:10.1088/1478-3975/ac4390.
21. **Ross TD**, **Coon BG**, **Yun S**, **Baeyens N**, **Tanaka K**, **Ouyang M**, **Schwartz MA.** Integrins in mechanotransduction. *Curr Opin Cell Biol* 25: 613–618, 2013. doi:10.1016/j.ceb.2013.05.006.
22. **Chen W**, **Lou J**, **Evans EA**, **Zhu C.** Observing force-regulated conformational changes and ligand dissociation from a single integrin on cells. *J Cell Biol* 199: 497–512, 2012. doi:10.1083/jcb.201201091.
23. **del Rio A**, **Perez-Jimenez R**, **Liu R**, **Roca-Cusachs P**, **Fernandez JM**, **Sheetz MP.** Stretching single talin rod molecules activates vinculin binding. *Science* 323: 638–641, 2009. doi:10.1126/science.1162912.
24. **Grashoff C**, **Hoffman BD**, **Brenner MD**, **Zhou R**, **Parsons M**, **Yang MT**, **McLean MA**, **Sligar SG**, **Chen CS**, **Ha T**, **Schwartz MA.** Measuring mechanical tension across vinculin reveals regulation of focal adhesion dynamics. *Nature* 466: 263–266, 2010. doi:10.1038/nature09198.

25. **Thodeti CK**, **Matthews B**, **Ravi A**, **Mammoto A**, **Ghosh K**, **Bracha AL**, **Ingber DE.** TRPV4 channels mediate cyclic strain-induced endothelial cell reorientation through integrin-to-integrin signaling. *Circ Res* 104: 1123–1130, 2009. doi:10.1161/CIRCRESAHA.108.192930.
26. **Volkers L**, **Mechioukhi Y**, **Coste B.** Piezo channels: from structure to function. *Pflugers Arch* 467: 95–99, 2015. doi:10.1007/s00424-014-1578-z.
27. **Chen X**, **Wanggou S**, **Bodalia A**, **Zhu M**, **Dong W**, **Fan JJ**, **Yin WC**, **Min HK**, **Hu M**, **Draghici D**, **Dou W**, **Li F**, **Coutinho FJ**, **Whetstone H**, **Kushida MM**, **Dirks PB**, **Song Y**, **Hui CC**, **Sun Y**, **Wang LY**, **Li X**, **Huang X.** A feedforward mechanism mediated by mechanosensitive ion channel $PIEZO_1$ and tissue mechanics promotes glioma aggression. *Neuron* 100: 799–815.e7, 2018. doi:10.1016/j.neuron.2018.09.046.
28. **Arcangeli A**, **Becchetti A.** Complex functional interaction between integrin receptors and ion channels. *Trends Cell Biol* 16: 631–639, 2006. doi:10.1016/j.tcb.2006.10.003.
29. **Lange K**, **Gartzke J.** F-actin-based Ca signaling-a critical comparison with the current concept of Ca signaling. *J Cell Physiol* 209: 270–287, 2006. doi:10.1002/jcp.20717.
30. **Leavesley DI**, **Schwartz MA**, **Rosenfeld M**, **Cheresh DA.** Integrin beta-1 and beta-3-mediated endothelial cell migration is triggered through distinct signaling mechanisms. *J Cell Biol* 121: 163–170, 1993. doi:10.1083/jcb.121.1.163.
31. **Schwartz MA.** Spreading of human endothelial cells on fibronectin or vitronectin triggers elevation of intracellular free calcium. *J Cell Biol* 120: 1003–1010, 1993. doi:10.1083/jcb.120.4.1003.
32. **Glogauer M**, **Arora P**, **Yao G**, **Sokholov I**, **Ferrier J**, **McCulloch CA.** Calcium ions and tyrosine phosphorylation interact coordinately with actin to regulate cytoprotective responses to stretching. *J Cell Sci* 110: 11–21, 1997. doi:10.1242/jcs.110.1.11.
33. **Becchetti A.** Ion channels and transporters in cancer. 1. Ion channels and cell proliferation in cancer. *Am J Physiol Cell Physiol* 301: C255–C265, 2011. doi:10.1152/ajpcell.00047.2011.
34. **Webb BA**, **Chimenti M**, **Jacobson MP**, **Barber DL.** Dysregulated pH: a perfect storm for cancer progression. *Nat Rev Cancer* 11: 671–677, 2011. doi:10.1038/nrc3110.
35. **Arcangeli A**, **Becchetti A**, **Del Bene MR**, **Wanke E**, **Olivotto M.** Fibronectin-integrin binding promotes hyperpolarization of murine erythroleukemia cells. *Biochem Biophys Res Commun* 177: 1266–1272, 1991. doi:10.1016/0006-291x(91)90678-z.
36. **Becchetti A**, **Arcangeli A**, **Del Bene MR**, **Olivotto M**, **Wanke E.** Response to fibronectin-integrin interaction in leukemia cells: delayed enhancing of a K^+ current. *Proc Biol Sci* 248: 235–240, 1992. doi:10.1098/rspb.1992.0067.
37. **Arcangeli A**, **Becchetti A**, **Mannini A**, **Mugnai G**, **De Filippi P**, **Tarone G**, **Del Bene MR**, **Barletta E**, **Wanke E**, **Olivotto M.** Integrin-mediated neurite outgrowth in neuroblastoma cells depends on the activation of potassium channels. *J Cell Biol* 122: 1131–1143, 1993. doi:10.1083/jcb.122.5.1131.
38. **Schwartz MA**, **Both G**, **Lechene C.** Effect of cell spreading on cytoplasmic pH in normal and transformed fibroblasts. *Proc Natl Acad Sci USA* 86: 4525–4529, 1989. doi:10.1073/pnas.86.12.4525.
39. **Demaurex N**, **Downey GP**, **Waddell TK**, **Grinstein S.** Intracellular pH regulation during spreading of human neutrophils. *J Cell Biol* 133: 1391–1402, 1996. doi:10.1083/jcb.133.6.1391.
40. **Davis MJ**, **Wu X**, **Nurkiewicz TR**, **Kawasaki J**, **Gui P**, **Hill MA**, **Wilson E.** Regulation of ion channels by integrins. *Cell Biochem Biophys* 36: 41–66, 2002. doi:10.1385/CBB:36:1:41.
41. **deHart GW**, **Jin T**, **McCloskey DE**, **Pegg AE**, **Sheppard D.** The $\alpha9\beta1$ integrin enhances cell migration by polyamine-mediated modulation of an inward-rectifier potassium channel. *Proc Natl Acad Sci USA* 105: 7188–7193, 2008. doi:10.1073/pnas.0708044105.
42. **Artym VV**, **Petty HR.** Molecular proximity of Kv1.3 voltage-gated potassium channels and β_1-integrins on the plasma membrane of melanoma cells: effects of cell adherence and channel blockers. *J Gen Physiol* 120: 29–37, 2002. doi:10.1085/jgp.20028607.
43. **Cherubini A**, **Hofmann G**, **Pillozzi S**, **Guasti L**, **Crociani O**, **Cilia E**, **Balzi M**, **Degani S**, **Di Stefano P**, **Defilippi P**, **Wanke E**, **Becchetti A**, **Olivotto M**, **Wymore R**, **Arcangeli AK.** 1 channels are physically linked to β_1 integrins and modulate adhesion-dependent signaling. *Mol Biol Cell* 16: 2972–2983, 2005. doi:10.1091/mbc.e04-10-0940.
44. **Cherubini A**, **Pillozzi S**, **Hofmann G**, **Crociani O**, **Guasti L**, **Lastraioli E**, **Polvani S**, **Masi A**, **Becchetti A**, **Wanke E**, **Olivotto M**, **Arcangeli A.** KV11.1 K^+ channels and β_1 integrins interact through the assembly of a macromolecular complex. *Ann N Y Acad Sci* 973: 559–561, 2002. doi:10.1111/j.1749-6632.2002.tb04701.x.
45. **Levite M**, **Cahalon L**, **Peretz A**, **Hershkoviz R**, **Sobko A**, **Ariel A**, **Desai R**, **Attali B**, **Lider O.** Extracellular K^+ and opening of voltage-gated potassium channels activate T cell integrin function: physical and functional association between Kv1.3 channels and β_1 integrins. *J Exp Med* 191: 1167–1176, 2000. doi:10.1084/jem.191.7.1167.
46. **Chudakova DA**, **Zeidan YH**, **Wheeler BW**, **Yu J**, **Novgorodov SA**, **Kindy MS**, **Hannun YA**, **Gudz TI.** Integrin-associated Lyn kinase promotes cell survival by suppressing acid sphingomyelinase activity. *J Biol Chem* 283: 28806–28816, 2008. doi:10.1074/jbc.M803301200.
47. **Pozo K**, **Cingolani LA**, **Bassani S**, **Laurent F**, **Passafaro M**, **Goda Y.** β_3 integrin interacts directly with GluA2 AMPA receptor subunit and regulates AMPA receptor expression in hippocampal neurons. *Proc Natl Acad Sci USA* 109: 1323–1328, 2012. doi:10.1073/pnas.1113736109.
48. **Becchetti A**, **Pillozzi S**, **Morini R**, **Nesti E**, **Arcangeli A.** New insights into the regulation of ion channels by integrins. *Int Rev Cell Mol Biol* 279: 135–190, 2010. doi:10.1016/S1937-6448(10)79005-5.
49. **Pillozzi S**, **Brizzi MF**, **Bernabei PA**, **Bartolozzi B**, **Caporale R**, **Basile V**, **Boddi V**, **Pegoraro L**, **Becchetti A**, **Arcangeli A.** VEGFR-1 (FLT-1), β_1 integrin and Kv11.1 K^+ channel form a macromolecular signaling complex in acute myeloid leukemia: role in cell migration and clinical outcome. *Blood* 110: 1238–1250, 2007. doi:10.1182/blood-2006-02-003772.
50. **Yu W**, **Gowda M**, **Sharad Y**, **Singh SA**, **Sesti F.** Oxidation of KCNB1 potassium channels triggers apoptotic integrin signaling in the brain. *Cell Death Dis* 8: e2737, 2017 [Erratum in *Cell Death Dis* 10: 756, 2019]. doi:10.1038/cddis.2017.160.
51. **Yu W**, **Shin MR**, **Sesti F.** Complexes formed with integrin-$\alpha5$ and KCNB1 potassium channel wild type or epilepsy-susceptibility variants modulate cellular plasticity via Ras and Akt signaling. *FASEB J* 33: 14680–14689, 2019. doi:10.1096/fj.201901792R.
52. **Birkner K**, **Wasser B**, **Ruck T**, **Thalman C**, **Luchtman D**, **Pape K**, **Schmaul S**, **Bitar L**, **Krämer-Albers EM**, **Stroh A**, **Meuth SG**, **Zipp F**, **Bittner S.** β1-Integrin- and KV1.3 channel-dependent signaling stimulates glutamate release from Th17 cells. *J Clin Invest* 130: 715–732, 2020. doi:10.1172/JCI126381.
53. **Nitkin RM**, **Smith MA**, **Magill C**, **Fallon JR**, **Yao YM**, **Wallace BG**, **McMahan UJ.** Identification of agrin, a synaptic organizing protein from *Torpedo* electric organ. *J Cell Biol* 105: 2471–2478, 1987. doi:10.1083/jcb.105.6.2471.
54. **Martin PT**, **Sanes JR.** Integrins mediate adhesion to agrin and modulate agrin signaling. *Development* 124: 3909–3917, 1997. doi:10.1242/dev.124.19.3909.
55. **Swenarchuk LE.** Nerve, muscle, and synaptogenesis. *Cells* 8: 1448, 2019. doi:10.3390/cells8111448.
56. **Nishimune H**, **Sanes JR**, **Carlson SS.** A synaptic laminin-calcium channel interaction organizes active zones in motor nerve terminals. *Nature* 432: 580–587, 2004. doi:10.1038/nature03112.
57. **Carlson SS**, **Valdez G**, **Sanes JR.** Presynaptic calcium channels and $\alpha3$-integrins are complexed with synaptic cleft laminins, cytoskeletal elements and active zone components. *J Neurochem* 115: 654–666, 2010. doi:10.1111/j.1471-4159.2010.06965.x.
58. **Lin B**, **Arai AC**, **Lynch G**, **Gall CM.** Integrins regulate NMDA receptor-mediated synaptic currents. *J Neurophysiol* 89: 2874–2878, 2003. doi:10.1152/jn.00783.2002.
59. **Shi Y**, **Ethell IM.** Integrins control dendritic spine plasticity in hippocampal neurons through NMDA receptor and Ca^{2+}/calmodulin-dependent protein kinase II-mediated actin reorganization. *J Neurosci* 26: 1813–1822, 2006. doi:10.1523/JNEUROSCI.4091-05.2006.
60. **Cingolani LA**, **Thalhammer A**, **Yu LM**, **Catalano M**, **Ramos T**, **Colicos MA**, **Goda Y.** Activity-dependent regulation of synaptic AMPA receptor composition and abundance by $\beta3$ integrins. *Neuron* 58: 749–762, 2008. doi:10.1016/j.neuron.2008.04.011.
61. **Jaudon F**, **Thalhammer A**, **Cingolani LA.** Integrin adhesion in brain assembly: from molecular structure to neuropsychiatric disorders. *Eur J Neurosci* 53: 3831–3850, 2021. doi:10.1111/ejn.14859.
62. **Park YK**, **Goda Y.** Integrins in synapse regulation. *Nat Rev Neurosci* 17: 745–756, 2016. doi:10.1038/nrn.2016.138.
63. **Vandenberg JI**, **Perry MD**, **Perrin MJ**, **Mann SA**, **Ke Y**, **Hill AP.** hERG K(+) channels: structure, function, and clinical significance. *Physiol Rev* 92: 1393–1478, 2012. doi:10.1152/physrev.00036.2011.

64. **Mitcheson J**, **Arcangeli A.** The therapeutic potential of hERG1 K^+ channels for treating cancer and cardiac arrhythmias. In: *Ion Channel Drug Discovery*, edited by Cox B, Gosling M. RSC Publishing, 2015, vol. 39, p. 258–296.
65. **Sanguinetti MC**, **Jiang C**, **Curran ME**, **Keating MT.** A mechanistic link between an inherited and an acquired cardiac arrhythmia: HERG encodes the IKr potassium channel. *Cell* 81: 299–307, 1995. doi:10.1016/0092-8674(95)90340-2.
66. **Bauer CK**, **Schäfer R**, **Schiemann D**, **Reid G**, **Hanganu I**, **Schwarz JR.** A functional role o the erg-like inward-rectifying K+ current in prolactin secretion from rat lactotrophs. *Mol Cell Endocrinol* 148: 37–45, 1999. doi:10.1016/S0303-7207(98)00241-X.
67. **Gullo F**, **Ales E**, **Rosati B**, **Lecchi M**, **Masi A**, **Guasti L**, **Cano-Abad MF**, **Arcangeli A**, **Lopez MG**, **Wanke E.** ERG K^+ channel blockade enhances firing and epinephrine secretion in rat chromaffin cells: the missing link to LQT2-related sudden death? *FASEB J* 17: 330–332, 2003. doi:10.1096/fj.02-0200fje.
68. **Chiesa N**, **Rosati B**, **Arcangeli A**, **Olivotto M**, **Wanke E.** A novel role for hERG K^+ channels: spike-frequency adaptation. *J Physiol* 501: 313–318, 1997 [Erratum in *J Physiol (Lond)* 502: 715, 1997].doi:10.1111/j.1469-7793.1997.313bn.x.
69. **Bauer CK**, **Schwarz JR.** Ether-á-go-go K^+ channels: effective modulators of neuronal excitability. *J Physiol* 596: 769–783, 2018. doi:10.1113/JP275477.
70. **Mewe M**, **Wulfsen I**, **Schuster AM**, **Middendorff R**, **Glassmeier G**, **Schwarz JR**, **Bauer CK.** Erg K^+ channels modulate contractile activity in the bovine epididymal duct. *Am J Physiol Regul Integr Comp Physiol* 294: R895–R904, 2008. doi:10.1152/ajpregu.00521.2007.
71. **Becchetti A**, **Crescioli S**, **Zanieri F**, **Petroni G**, **Mercatelli R**, **Coppola S**, **Gasparoli L**, **D'Amico M**, **Pillozzi S**, **Crociani O**, **Stefanini M**, **Fiore A**, **Carraresi L**, **Morello V**, **Manoli S**, **Brizzi MF**, **Ricci D**, **Rinaldi M**, **Masi A**, **Schmidt T**, **Quercioli F**, **Defilippi P**, **Arcangeli A.** The conformational state of Kv11.1 channels determines integrin association, downstream signaling, and cancer progression. *Sci Signal* 10: eaaf3236, 2017. doi:10.1126/scisignal.aaf3236.
72. **Duranti C**, **Iorio J**, **Lottini T**, **Lastraioli E**, **Crescioli S**, **Bagni G**, **Lulli M**, **Capitani C**, **Bouazzi R**, **Stefanini M**, **Carraresi L**, **Iamele L**, **De Jonge H**, **Arcangeli A.** Harnessing the hERG1/β_1 integrin complex via a novel bispecific single-chain antibody: an effective strategy against solid cancers. *Mol Cancer Ther* 20: 1338–1349, 2021. doi:10.1158/1535-7163.MCT-20-1111.
73. **Franco D**, **Demolombe S**, **Kupershmidt S**, **Dumaine R**, **Dominguez JN**, **Roden D**, **Antzelevitch C**, **Escande D**, **Moorman AF.** Divergent expression of delayed rectifier K^+ channel subunits during mouse heart development. *Cardiovasc Res* 52: 65–75, 2001. doi:10.1016/s0008-6363(01)00349-2.
74. **Polvani S**, **Masi A**, **Pillozzi S**, **Gragnani L**, **Crociani O**, **Olivotto M**, **Becchetti A**, **Wanke E**, **Arcangeli A.** Developmentally regulated expression of the mouse homologues of the potassium channel encoding genes m-erg1, m-erg2 and m-erg3. *Gene Expr Patterns* 3: 767–776, 2003. doi:10.1016/s1567-133x(03)00124-8.
75. **de Castro MP**, **Aránega A**, **Franco D.** Protein distribution of Kcnq1, Kcnh2, and Kcne3 potassium channel subunits during mouse embryonic development. *Anat Rec A Discov Mol Cell Evol Biol* 288: 304–315, 2006. doi:10.1002/ar.a.20312.
76. **Guasti L**, **Cilia E**, **Crociani O**, **Hofmann G**, **Polvani S**, **Becchetti A**, **Wanke E**, **Tempia F**, **Arcangeli A.** Expression pattern of the ether-á-go-go-related (ERG) family proteins in the adult mouse central nervous system: evidence for coassembly of different subunits. *J Comp Neurol* 491: 157–174, 2005. doi:10.1002/cne.20721.
77. **Papa M**, **Boscia F**, **Canitano A**, **Castaldo P**, **Sellitti S**, **Annunziato L**, **Taglialatela M.** Expression pattern of the ether-á-go-go-related (ERG) K^+ channel-encoding genes ERG1, ERG2, and ERG3 in the adult rat central nervous system. *J Comp Neurol* 466: 119–135, 2003. doi:10.1002/cne.10886.
78. **Saganich MJ**, **Machado E**, **Rudy B.** Differential expression of genes encoding subthreshold-operating voltage-gated K^+ channels in brain. *J Neurosci* 21: 4609–4624, 2001. doi:10.1523/JNEUROSCI.21-13-04609.2001.
79. **Teng GQ**, **Zhao X**, **Lees-Miller JP**, **Quinn FR**, **Li P**, **Rancourt DE**, **London B**, **Cross JC**, **Duff HJ.** Homozygous missense N629D hERG (KCNH2) potassium channel mutation causes developmental defects in the right ventricle and its outflow tract and embryonic lethality. *Circ Res* 103: 1483–1491, 2008. doi:10.1161/CIRCRESAHA.108.177055.
80. **Teng G**, **Zhao X**, **Lees-Miller JP**, **Belke D**, **Shi C**, **Chen Y**, **O'Brien ER**, **Fedak PW**, **Bracey N**, **Cross JC**, **Duff HJ.** Role of mutation and pharmacologic block of human KCNH2 in vasculogenesis and fetal mortality. *Circ Arrhythm Electrophysiol* 8: 420–428, 2015. doi:10.1161/CIRCEP.114.001837.
81. **Crociani O**, **Cherubini A**, **Piccini E**, **Polvani S**, **Costa L**, **Fontana L**, **Hofmann G**, **Rosati B**, **Wanke E**, **Olivotto M**, **Arcangeli A.** erg gene (s) expression during development of the nervous and muscular system of quail embryos. *Mech Dev* 95: 239–243, 2000. doi:10.1016/s0925-4773(00)00335-x.
82. **Arcangeli A**, **Rosati B**, **Cherubini A**, **Crociani O**, **Fontana L**, **Ziller C**, **Wanke E**, **Olivotto M.** hERG- and IRK-like inward rectifier currents are sequentially expressed during neuronal development of neural crest cells and their derivatives. *Eur J Neurosci* 9: 2596–2604, 1997. doi:10.1111/j.1460-9568.1997.tb01689.x.
83. **Olsen ML**, **Sontheimer H.** Mislocalization of Kir channels in malignant glia. *Glia* 46: 63–73, 2004. doi:10.1002/glia.10346.
84. **Masi A**, **Becchetti A**, **Restano-Cassulini R**, **Polvani S**, **Hofmann G**, **Buccoliero AM**, **Paglierani M**, **Pollo B**, **Taddei GL**, **Gallina P**, **Di Lorenzo N**, **Franceschetti S**, **Wanke E**, **Arcangeli A.** hERG1 channels are overexpressed in glioblastoma multiforme and modulate VEGF secretion in glioblastoma cell lines. *Br J Cancer* 93: 781–792, 2005. doi:10.1038/sj.bjc.6602775.
85. **Becchetti A**, **De Fusco M**, **Crociani O**, **Cherubini A**, **Restano-Cassulini R**, **Lecchi M**, **Masi A**, **Arcangeli A**, **Casari G**, **Wanke E.** The functional properties of the human ether-á-go-go-like (HELK2) K^+ channel. *Eur J Neurosci* 16: 415–428, 2002. doi:10.1046/j.1460-9568.2002.02079.x.
86. **Afrasiabi E**, **Hietamäki M**, **Viitanen T**, **Sukumaran P**, **Bergelin N**, **Törnquist K.** Expression and significance of hERG (KCNH2) potassium channels in the regulation of MDA-MB-435S melanoma cell proliferation and migration. *Cell Signal* 22: 57–64, 2010. doi:10.1016/j.cellsig.2009.09.010.
87. **Crociani O**, **Zanieri F**, **Pillozzi S**, **Lastraioli E**, **Stefanini M**, **Fiore A**, **Fortunato A**, **D'Amico M**, **Masselli M**, **De Lorenzo E**, **Gasparoli L**, **Chiu M**, **Bussolati O**, **Becchetti A**, **Arcangeli A.** $hERG_1$ channels modulate integrin signaling to trigger angiogenesis and tumor progression in colorectal cancer. *Sci Rep* 3: 3308, 2013. doi:10.1038/srep03308.
88. **Manoli S**, **Coppola S**, **Duranti C**, **Lulli M**, **Magni L**, **Kuppalu N**, **Nielsen N**, **Schmidt T**, **Schwab A**, **Becchetti A**, **Arcangeli A.** The activity of Kv 11.1 potassium channel modulates f-actin organization during cell migration of pancreatic ductal adenocarcinoma cells. *Cancers* 11: 135, 2019. doi:10.3390/cancers11020135.
89. **Muratori L**, **Petroni G**, **Antonuzzo L**, **Boni L**, **Iorio J**, **Lastraioli E**, **Bartoli G**, **Messerini L**, **Di Costanzo F**, **Arcangeli A.** hERG1 positivity and Glut-1 negativity identifies high-risk TNM stage I and II colorectal cancer patients, regardless of adjuvant chemotherapy. *Onco Targets Ther* 9: 6325–6332, 2016. doi:10.2147/OTT.S114090.
90. **Pillozzi S**, **Brizzi MF**, **Balzi M**, **Crociani O**, **Cherubini A**, **Guasti L**, **Bartolozzi B**, **Becchetti A**, **Wanke E**, **Bernabei PA**, **Olivotto M**, **Pegoraro L**, **Arcangeli A.** hERG potassium channels are constitutively expressed in primary human acute myeloid leukemias and regulate cell proliferation of normal and leukemic hemopoietic progenitors. *Leukemia* 16: 1791–1798, 2002. doi:10.1038/sj.leu.2402572.
91. **Wang H**, **Zhang Y**, **Cao L**, **Han H**, **Wang J**, **Yang B**, **Nattel S**, **Wang Z.** HERG K^+ channel, a regulator of tumor cell apoptosis and proliferation. *Cancer Res* 62: 4843–4848, 2002.
92. **Zhang R**, **Tian P**, **Chi Q**, **Wang J**, **Wang Y**, **Sun L**, **Liu Y**, **Tian S**, **Zhang Q.** Human *ether-á-go-go*-related gene expression is essential for cisplatin to induce apoptosis in human gastric cancer. *Oncol Rep* 27: 433–440, 2012. doi:10.3892/or.2011.1515.
93. **Menéndez ST**, **Villaronga MÁ**, **Rodrigo JP**, **Álvarez-Teijeiro S**, **Urdinguio RG**, **Fraga MF**, **Suárez C**, **García-Pedrero JM.** HERG1A potassium channel is the predominant isoform in head and neck squamous cell carcinomas: evidence for regulation by epigenetic mechanisms. *Sci Rep* 6: 19666, 2016. doi:10.1038/srep19666.
94. **Fernández-Valle Á**, **Rodrigo JP**, **Rodríguez-Santamarta T**, **Villaronga MÁ**, **Álvarez-Teijeiro S**, **García-Pedrero JM**, **Suárez-Fernández L**, **Lequerica-Fernández P**, **de Vicente JC.** HERG1 potassium channel expression in potentially malignant disorders of the

oral mucosa and prognostic relevance in oral squamous cell carcinoma. *Head Neck* 38: 1672–1678, 2016. doi:10.1002/hed.24493.

95. **Wei X**, **Sun H**, **Yan H**, **Zhang C**, **Zhang S**, **Liu X**, **Hua N**, **Ma X**, **Zheng J.** ZC88, a novel 4-amino piperidine analog, inhibits the growth of neuroblastoma cells through blocking hERG potassium channels. *Cancer Biol Ther* 14: 450–457, 2013. doi:10.4161/cbt.24423.
96. **Glassmeier G**, **Hempel K**, **Wulfsen I**, **Bauer CK**, **Schumacher U**, **Schwarz JR.** Inhibition of HERG1 K + channel protein expression decreases cell proliferation of human small cell lung cancer cells. *Pflugers Arch* 463: 365–376, 2012. doi:10.1007/s00424-011-1045-z.
97. **Lastraioli E**, **Perrone G**, **Sette A**, **Fiore A**, **Crociani O**, **Manoli S**, **D'Amico M**, **Masselli M**, **Iorio J**, **Callea M**, **Borzomati D**, **Nappo G**, **Bartolozzi F**, **Santini D**, **Bencini L**, **Farsi M**, **Boni L**, **Di Costanzo F**, **Schwab A**, **Onetti Muda A**, **Coppola R**, **Arcangeli A.** hERG1 channels drive tumour malignancy and may serve as prognostic factor in pancreatic ductal adenocarcinoma. *Br J Cancer* 112: 1076–1087, 2015. doi:10.1038/bjc.2015.28.
98. **Lastraioli E**, **Guasti L**, **Crociani O**, **Polvani S**, **Hofmann G**, **Witchel H**, **Bencini L**, **Calistri M**, **Messerini L**, **Scatizzi M**, **Moretti R**, **Wanke E**, **Olivotto M**, **Mugnai G**, **Arcangeli A.** herg1 gene and HERG1 protein are overexpressed in colorectal cancers and regulate cell invasion of tumor cells. *Cancer Res* 64: 606–611, 2004. doi:10.1158/0008-5472.can-03-2360.
99. **Lastraioli E**, **Bencini L**, **Bianchini E**, **Romoli MR**, **Crociani O**, **Giommoni E**, **Messerini L**, **Gasperoni S**, **Moretti R**, **Di Costanzo F**, **Boni L**, **Arcangeli A.** hERG1 channels and glut-1 as independent prognostic indicators of worse outcome in stage i and ii colorectal cancer: a pilot study. *Transl Oncol* 5: 105–112, 2012. doi:10.1593/tlo.11250.
100. **Arcangeli A**, **Di Costanzo F**, **Antonuzzo L**, **Messerini L**, **Lastraioli E**, **Iorio J**, **Petroni G**, **Boni L**, **Tofani L**, **Coppola R**, **Perrone G**, **Caputo D**, **Francesconi M.** Predictive power of hERG1 potassium channel expression for response to Bevacizumab in metastatic in colorectal cancer patients. *Proceedings of the EACR AACR SIC 2017*. Florence, Italy, June 24–27, 2017.
101. **Iorio J**, **Duranti C**, **Lottini T**, **Lastraioli E**, **Bagni G**, **Becchetti A**, **Arcangeli A.** $K_V11.1$ potassium channels and the Na^+/H^+ antiporter NHE1 modulate adhesion-dependent intracellular pH in colorectal cancer cells. *Front Pharmacol* 11: 848, 2020. doi:10.3389/fphar.2020.00848.
102. **Lastraioli E**, **Lottini T**, **Iorio J**, **Freschi G**, **Fazi M**, **Duranti C**, **Carraresi L**, **Messerini L**, **Taddei A**, **Ringressi MN**, **Salemme M**, **Villanacci V**, **Vindigni C**, **Tomezzoli A**, **La Mendola R**, **Bencivenga M**, **Compagnoni B**, **Chiudinelli M**, **Saragoni L**, **Manzi I**, **De Manzoni G**, **Bechi P**, **Boni L**, **Arcangeli A.** hERG1 behaves as biomarker of progression to adenocarcinoma in Barrett's esophagus and can be exploited for a novel endoscopic surveillance. *Oncotarget* 7: 59535–59547, 2016. doi:10.18632/oncotarget.11149.
103. **Shao XD**, **Wu KC**, **Guo XZ**, **Xie MJ**, **Zhang J**, **Fan DM.** Expression and significance of HERG protein in gastric cancer. *Cancer Biol Ther* 7: 45–50, 2008. doi:10.4161/cbt.7.1.5126.
104. **Ding XW**, **Yang WB**, **Gao S**, **Wang W**, **Li Z**, **Hu WM**, **Li JJ**, **Luo HS.** Prognostic significance of hERG1 expression in gastric cancer. *Dig Dis Sci* 55: 1004–1010, 2010. doi:10.1007/s10620-009-0834-0.
105. **Crociani O**, **Lastraioli E**, **Boni L**, **Pillozzi S**, **Romoli MR**, **D'Amico M**, **Stefanini M**, **Crescioli S**, **Masi A**, **Taddei A**, **Bencini L**, **Bernini M**, **Farsi M**, **Beghelli S**, **Scarpa A**, **Messerini L**, **Tomezzoli A**, **Vindigni C**, **Morgagni P**, **Saragoni L**, **Giommoni E**, **Gasperoni S**, **Di Costanzo F**, **Roviello F**, **De Manzoni G**, **Bechi P**, **Arcangeli A.** hERG1 channels regulate VEGF-A secretion in human gastric cancer: clinicopathological correlations and therapeutical implications. *Clin Cancer Res* 20: 1502–1512, 2014 [Erratum in *Clin Cancer Res* 20: 4168–4169, 2014]. doi:10.1158/1078-0432.CCR-13-2633.
106. **Feng J**, **Yu J**, **Pan X**, **Li Z**, **Chen Z**, **Zhang W**, **Wang B**, **Yang L**, **Xu H**, **Zhang G**, **Xu Z.** HERG1 functions as an oncogene in pancreatic cancer and is downregulated by miR-96. *Oncotarget* 5: 5832–5844, 2014. doi:10.18632/oncotarget.2200.
107. **Zhi D**, **Zhao X**, **Dong M**, **Yan C.** miR-493 inhibits proliferation and invasion in pancreatic cancer cells and inversely regulated hERG1 expression. *Oncol Lett* 14: 7398–7404, 2017. doi:10.3892/ol.2017.7178.
108. **Iorio J**, **Meattini I**, **Bianchi S**, **Bernini M**, **Maragna V**, **Dominici L**, **Casella D**, **Vezzosi V**, **Orzalesi L**, **Nori J**, **Livi L**, **Arcangeli A**, **Lastraioli E.** hERG1 channel expression associates with molecular subtypes and prognosis in breast cancer. *Cancer Cell Int* 18: 93, 2018. doi:10.1186/s12935-018-0592-1.
109. **Cherubini A**, **Taddei GL**, **Crociani O**, **Paglierani M**, **Buccoliero AM**, **Fontana L**, **Noci I**, **Borri P**, **Borrani E**, **Giachi M**, **Becchetti A**, **Rosati B**, **Wanke E**, **Olivotto M**, **Arcangeli A.** HERG potassium channels are more frequently expressed in human endometrial cancer as compared to non-cancerous endometrium. *Br J Cancer* 83: 1722–1729, 2000. doi:10.1054/bjoc.2000.1497.
110. **Asher V**, **Khan R**, **Warren A**, **Shaw R**, **Schalkwyk GV**, **Bali A**, **Sowter HM.** The Eag potassium channel as a new prognostic marker in ovarian cancer. *Diagn Pathol* 5: 78, 2010. doi:10.1186/1746-1596-5-78.
111. **Asher V**, **Warren A**, **Shaw R**, **Sowter H**, **Bali A**, **Khan R.** The role of Eag and HERG channels in cell proliferation and apoptotic cell death in SK-OV-3 ovarian cancer cell line. *Cancer Cell Int* 11: 6, 2011. doi:10.1186/1475-2867-11-6.
112. **Cicek MS**, **Koestler DC**, **Fridley BL**, **Kalli KR**, **Armasu SM**, **Larson MC**, **Wang C**, **Winham SJ**, **Vierkant RA**, **Rider DN**, **Block MS**, **Klotzle B**, **Konecny G**, **Winterhoff BJ**, **Hamidi H**, **Shridhar V**, **Fan JB**, **Visscher DW**, **Olson JE**, **Hartmann LC**, **Bibikova M**, **Chien J**, **Cunningham JM**, **Goode EL.** Epigenome-wide ovarian cancer analysis identifies a methylation profile differentiating clear-cell histology with epigenetic silencing of the HERG K^+ channel. *Hum Mol Genet* 22: 3038–3047, 2013. doi:10.1093/hmg/ddt160.
113. **Arcangeli A**, **Romoli MR**, **Boni L**, **Gerlini G**, **Tofani L**, **Urso C**, **Borgognoni L.** High hERG1 expression in advanced melanoma. *Melanoma Res* 23: 185–190, 2013. doi:10.1097/CMR.0b013e32835fc6c9.
114. **Zeng W**, **Liu Q**, **Chen Z**, **Wu X**, **Zhong Y**, **Wu J.** Silencing of hERG1 gene inhibits proliferation and invasion, and induces apoptosis in human osteosarcoma cells by targeting the NF-κB pathway. *J Cancer* 7: 746–757, 2016. doi:10.7150/jca.13289.
115. **Becchetti A**, **Petroni G**, **Arcangeli A.** Ion channel conformations regulate integrin-dependent signaling. *Trends Cell Biol* 29: 298–307, 2019. doi:10.1016/j.tcb.2018.12.005.
116. **Hofmann G**, **Bernabei PA**, **Crociani O**, **Cherubini A**, **Guasti L**, **Pillozzi S**, **Lastraioli E**, **Polvani S**, **Bartolozzi B**, **Solazzo V**, **Gragnani L**, **Defilippi P**, **Rosati B**, **Wanke E**, **Olivotto M**, **Arcangeli A.** HERG K + channels activation during β_1 integrin-mediated adhesion to fibronectin induces an up-regulation of $\alpha_v\beta_3$ integrin in the preosteoclastic leukemia cell line FLG 29.1. *J Biol Chem* 276: 4923–4931, 2001. doi:10.1074/jbc.M005682200.
117. **Petroni G**, **Bagni G**, **Iorio J**, **Duranti C**, **Lottini T**, **Stefanini M**, **Kragol G**, **Becchetti A**, **Arcangeli A.** Clarithromycin inhibits autophagy in colorectal cancer by regulating the hERG1 potassium channel interaction with PI3K. *Cell Death Dis* 11: 161, 2020 [Erratum in *Cell Death Dis* 11: 209, 2020]. doi:10.1038/s41419-020-2349-8.
118. **Pillozzi S**, **Masselli M**, **De Lorenzo E**, **Accordi B**, **Cilia E**, **Crociani O**, **Amedei A**, **Veltroni M**, **D'Amico M**, **Basso G**, **Becchetti A**, **Campana D**, **Arcangeli A.** Chemotherapy resistance in acute lymphoblastic leukemia requires hERG1 channels and is overcome by hERG1 blockers. *Blood* 117: 902–914, 2011. doi:10.1182/blood-2010-01-262691.
119. **Lastraioli E**, **Pillozzi S**, **Mari A**, **Tellini R**, **Duranti C**, **Baldazzi V**, **Venturini S**, **Minervini A**, **Lapini A**, **Nesi G**, **Carini M**, **Arcangeli A.** hERG1 and CA IX expression are associated with disease recurrence in surgically resected clear cell renal carcinoma. *Eur J Surg Oncol* 46: 209–215, 2020. doi:10.1016/j.ejso.2019.10.031.
120. **Sterling P**, **Laughlin S.** *Principles of Neural Design*. Cambridge, MA: MIT Press, 2015.
121. **Mahns DA**, **Perkins NM**, **Sahai V**, **Robinson L**, **Rowe MJ.** Vibrotactile frequency discrimination in human hairy skin. *J Neurophysiol* 95: 1442–1450, 2006. doi:10.1152/jn.00483.2005.
122. **Torre V**, **Ashmore JF**, **Lamb TD**, **Menini A.** Transduction and adaptation in sensory receptor cells. *J Neurosci* 15: 7757–7768, 1995. doi:10.1523/JNEUROSCI.15-12-07757.
123. **Andersen OS**, **Koeppe IIR.** Molecular determinants of channel function. *Physiol Rev* 72: S89–S158, 1992. doi:10.1152/physrev.1992.72.suppl_4.S89.
124. **Duranti C**, **Arcangeli A.** Ion channel targeting with antibodies and antibody fragments for cancer diagnosis. *Antibodies* 8: 33, 2019. doi:10.3390/antib8020033.

125. **Duranti C**, **Iorio J**, **Bagni G**, **Lottini T**, **Lastraioli E**, **Capitani C**, **Lulli M**, **Chandavarkar R**, **Arcangeli A.** Targeting ion channel and transporter macromolecular hubs: a novel approach to overcome therapy resistance in cancer. SIPMeT Young Scientist Meeting: "MOLECULAR PATHOLOGY:FROM BENCH TO BEDSIDE", 10–11 December 2021, Perugia, Italy.

126. **Duranti C**, **Carraresi L**, **Sette A**, **Stefanini M**, **Lottini T**, **Crescioli S**, **Crociani O**, **Iamele L**, **De Jonge H**, **Gherardi E**, **Arcangeli A.** Generation and characterization of novel recombinant anti-hERG1 scFv antibodies for cancer molecular imaging. *Oncotarget* 9: 34972–34989, 2018. doi:10.18632/oncotarget.26200.