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Viral dependence on cellular ion channels - an emerging anti-viral target?

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Abstract

The broad range of cellular functions governed by ion channels represents an attractive target for viral manipulation. Indeed, modulation of host cell ion channel activity by viral proteins is being increasingly identified as an important virus-host interaction. Recent examples have demonstrated that virion entry, virus-egress and the maintenance of a cellular environment conducive to virus persistence are in part, dependent on virus manipulation of ion channel activity. Most excitingly, evidence has emerged that targeting ion channels pharmacologically can impede virus lifecycles. Here we discuss current examples of virus-ion channel interactions and the potential of targeting ion channel function as a new, pharmacologically safe and broad ranging anti-viral therapeutic strategy.

Introduction

Ion channels are multi-subunit, pore-forming membrane proteins that catalyse the rapid and selective passage of inorganic ions across all cell membranes. The “channelome” consists of over 300 ion channel subunits expressed per cell [1]. Initially characterised for their control of action potential propagation in “excitable” cells such as cardiac and neuronal tissue, it is now appreciated that ion channels are expressed ubiquitously in all cell types, including non-excitable cells. Within these cells, ion channels localise to the plasma membrane and the membranes of subcellular organelles, controlling cellular ion homeostasis in response to a range of extracellular and intracellular stimuli. The activity of ion channels is dictated by both their cellular distribution and opening probability. The controlled trafficking of ion channels has been extensively researched and reviewed in Balse et al (2012) [2]. Key regulators of opening probability include the phosphorylation of key ion channel residues that switch channel activity on or off. Accordingly, many ion channel subunits are complexed to signalling receptors and/or cellular kinases.

Owing to their role in many critical cellular processes, it is unsurprising that channel dysfunction is associated with the progression of multiple diseases termed channelopathies (this is an extensive field and is reviewed in Kim (2014) [3]). Recent evidence has implicated ion channel-mediated control of the plasma membrane potential (particularly by K^+ channels) in the regulation of cell signalling processes, cell migration, apoptosis, cell volume and cell cycle progression [4]–[6]. Landmark studies within the last year addressed how plasma membrane depolarization (controlled through ion channel activity) influences signalling through depolarization-induced changes in phosphatidylserine and K-Ras plasma membrane spatiotemporal dynamics, ultimately influencing mitogenic signalling circuits. These findings may begin to explain why many ion channels are implicated in numerous disease states [7], [8] and accordingly, some 13% of currently licenced clinically available drugs are ion channel modulators. All viruses must exploit the environment of susceptible cells to replicate and survive. Many viruses encode their own ion channel, termed viroporins discussed in reviews by *Royle*

et al (2015) and *Sze and Tan* (2015) [9], [10]). Viroporins highlight the importance of the control of ion homeostasis during virus infection cycles, but it is noteworthy that many viruses have no known viroporin, and it is thus assumed they have adapted other mechanisms to manipulate the host cell ionic environment. In this regard, several viral proteins have been shown to directly or indirectly modulate cellular ion channel functionality (Figure 1). The main unanswered questions are how these interactions link to important viral processes and if they can be targeted for anti-viral strategies. These questions will be discussed in the sections below.

Ion channels and virus trafficking

As key regulators of membrane potential, ion channel functionality has been demonstrated to be a pre-requisite for virion entry and virus-host membrane fusion processes. Filoviruses, including Ebola virus (EBOV) and Marburg virus (MVB), enter cells through macropinocytosis [11]. Gehring *et al* (2014) revealed that treatment with the multi-ion channel inhibitors amiodarone and dronedarone, or the L-type voltage gated Ca^{2+} channel inhibitor verapamil (a drug clinically available for the treatment of hypertension) prevented filovirus entry, implicating Ca^{2+} channel activity as a requirement during virion entry processes [11]. Two-pore Ca^{2+} channels 1 (TPC1) and 2 (TPC2), were subsequently identified as the sub family of channels required for early stages of EBOV entry as treatment of cells with specific pharmacological inhibitors and TPC1/TPC2 gene silencing prevented EBOV release from the endocytic network (Figure 2A). It was further shown that TPC inhibition prevented EBOV capsid-mediated endosomal fusion and the inhibition of TPC function was similarly debilitating to MVB entry, representing a common regulatory mechanism for this virus family [12].

More recent work has demonstrated that K^+ channels are key regulators of Bunyamwera virus (BUNV) post-entry processes, the model virus of the *Bunyaviridae* family. BUNV was found to activate K^+ channels during the initial 6 hours of virus infection [13] and furthermore, K^+ channel inhibition during this lifecycle stage was shown to be detrimental to BUNV, identifying a requirement of K^+ channel functionality during events shortly after virus entry but prior to viral RNA synthesis [13]. This early time frame includes post-entry endosomal trafficking, viral-host membrane fusion and ribonucleoprotein (RNP) release prior to the formation of 'viral factories' at the Golgi (K^+ channels are likely required at the plasma membrane or within endosomal compartments; see Figure 2B. Using a rational panel of more specific K^+ channel pharmacological modulators, two-pore K^+ channels (K_{2P}) were implicated as the channel family required by BUNV [13]. Importantly, this requirement for K^+ channel function was shared with other bunyaviruses, including Schmallenberg virus and Hazara virus, implicating it as a potential virus-host interaction utilised by all bunyavirus family members [13].

Cl^- channels are a superfamily of poorly understood anion channels, but their functionality has been demonstrated as a requirement during herpes simplex virus-1 (HSV-1) entry. HSV-1 infection was shown to induce Cl^- influx and Cl^- channel inhibitors including tamoxifen and 5-nitro-2-(3-phenylpropylamino)-benzoate (NPPB) significantly hindered HSV-1 entry, including virion binding, penetration into the host cell and nuclear translocation. More specifically, Cl^- channel modulation was found to affect viral fusion processes by inhibiting viral protein binding to lipid rafts and interrupting Ca^{2+} homeostasis [14]. Since tamoxifen is a clinically available drug (though not entirely specific for

Cl^- channels), future studies assessing its effect on HSV-1 infection *in vivo* may reveal intriguing insights into its therapeutic potential for this virus family.

Ion channels and virus persistence

As obligate intracellular parasites, viruses require the maintenance of the host cell environment to complete their replication cycles. Hepatitis C virus (HCV) chronically infects hepatocytes and as such, has developed numerous mechanisms for maintaining the viability of infected host cells, primarily through the perturbation of numerous apoptotic stimuli, reviewed in [15]. One such mechanism involves the inhibition of a liver expressed voltage-gated K^+ channel 2.1 (Kv2.1) by the HCV non-structural NS5A protein [16]. In hepatocytes, oxidative stress induces phosphorylation and activation of Kv2.1, which traffics to the plasma membrane and produces an outward K^+ current that triggers apoptotic induction [17]. An increase in reactive oxygen species (ROS) has been identified in HCV (genotype 1b) infected hepatocytes, thus the virus would appear capable of triggering such channel activity. To circumvent this, HCV-NS5A prevents the oxidative-stress induced phosphorylation of Kv2.1 and associated apoptotic signalling when expressed alone, or in the context of the full complement of viral proteins [16]. Additionally, the mechanism of Kv2.1 inhibition in hepatocytes was shown to involve the suppression of p38 MAPK signalling [16], as depicted in Figure 3A. It was also revealed that NS5A inhibits stress-mediated neuronal cell death through the inhibition of Kv2.1 activation via Src-mediated phosphorylation [17]. It is likely that HCV thus perturbs Kv2.1 activation to bypass ROS-mediated apoptosis to allow virus persistence and survival [18]. In addition to regulating Kv2.1 currents, HCV was found to increase intracellular hepatic Cl^- influx that can be inhibited by selective Cl^- channel blockers [19]. Cl^- channel silencing in infected hepatocytes revealed three liver expressed Cl^- channels (ClC-1, ClC-5 and ClC-7) that were required for HCV replication, suggesting Cl^- flux plays an important but uncharacterised role in the HCV lifecycle [19]. Interestingly inhibitors of K^+, Na^+ and Ca^{2+} channels did not affect HCV replication, suggesting a specific requirement for intracellular Cl^- accumulation during this lifecycle stage.

HIV-1 primarily exhibits tropism for CD4(+) T-lymphocytes (T cells) in which the HIV-1 accessory protein Nef has been shown to indirectly alter K^+ concentrations [20]. Further studies using inside-out patch clamping confirmed Nef-mediated inhibition of large-conductance Ca^{2+}-dependant K^+ channels (BKca) [21], [22], but the effects of BKca modulation during the HIV-1 lifecycle was not investigated [16]. HIV-1 gp120 and viral protein U (Vpu) have also been shown to affect K^+ channel activity, proposed to regulate HIV-1 particle release. Gp120 binding to the cytoplasmic C-terminus of the ether-a-go-go (hERG) K^+ channel and its subsequent inhibition enhanced virus particle release, which could be blocked by hERG channel overexpression [21]. HIV-1 Vpu was also reported to manipulate cellular resting membrane potentials through interference with background leak K^+ channels [23], [24]. *Hsu et al* (2004) identified that expression of the acid-sensitive K_{2P} channel TASK-1 inhibits HIV-1 release via an unknown mechanism [25]. Vpu facilitates HIV release through the formation of inactive Vpu/TASK-1 heterodimers (Figure 3B), inhibiting TASK-1 currents and destabilising the membrane potential to favour virus budding [25]. K^+ channel activity thus appears a key virus-host interaction

during HIV infection and how these perturbations ultimately impact on HIV infection requires further investigation.

Of the other reported ion channel virus interactions that mediate virus persistence, Monkeypox virus infection was shown to downregulate eight ion channels across key channel families (K^+, Na^+, Cl^- and Ca^{2+}), but the role of this modulation during virus infection was not characterised [26]. Epstein-Barr virus was found to initiate Ca^{2+} influx into endoplasmic reticulum stores altering Ca^{2+} homeostasis through the increased expression of the Orai1 channel, representing virus modulation of intracellular ion channel functionality [27]. Additionally human T cell leukaemia virus type 1 (HTLV-1) was shown to trigger an inward K^+ current for as yet unknown viral processes [28].

Viral modulation of ion channels in excitable cells

Neuronal firing

Ion channels are fundamental regulators of action potential generation and signal transduction in excitable cells, such as neurons. Chronic viral infection of the central nervous system (CNS) can lead to debilitating neurological diseases, possibily expedited through the modulation of ion channel activity. In mumps virus (MpV) infection, a reduction in the frequency and magnitude of action potentials, predicted to involve voltage-gated Na^+ (Nav) channel inhibition is observed [29]. Conversely, Varicella-zoster viruses (VZV), a known cause of post-herpetic neuralgia (PHN), was shown to induce changes in Nav channel currents known to be associated with neuropathic pain. PHN-associated VZV sodium current increases were shown to be mediated in part by the Nav 1.6 and Nav 1.7 members of this family [30]. Rabies virus (RABV) is also associated with symptoms characteristic of CNS alteration, including generalised convulsions, aggressiveness and restlessness [31]. Whole cell patch-clamp analysis identified reduced activity of Nav and inwardly-rectifying K^+ channels in infected mouse neuroblastoma cells, predicted to alter action potential firing [31]. Additionally, RABV was found to prevent the inhibition of the α_2-adrenoceptor-mediated Ca^{2+} current in the presence of noradrenaline, an important mediator of Ca^{2+} entry that signals neurotransmitter release. Interestingly, continuous activation of Ca^{2+} influx has been associated with increased aggressiveness in monkeys, a common symptom of RABV infection in infected animals [32], whereby α_2-adrenoceptor-mediated inhibition reduces neurotransmitter release under normal physiological conditions [33]. These effects of RABV on Na^+, K^+ and Ca^{2+} channel activity may somehow act to promote virus pathogenesis, with lethal consequences to the host [31]. In neuronal tissue, the Kv1.3 outward-rectifier K^+ channel was shown to be modulated by the HIV encoded Tat protein. [34]. HIV-Tat was found to increase the surface expression of Kv1.3 which accompanied microglial activation and Tat-induced neurotoxicity [35]. Other HIV-neuronal ion channel interactions include HIV-gp120, that stimulates an outward K^+ conductance mediated by BKca and Kv2.1 channels [35], [36]. As discussed, Kv2.1 activation leads to neuronal apoptosis and accordingly Kv2.1 inhibition could prevent gp120-mediated K^+ efflux and related apoptotic cell death [35].

Cardiac rhythm

The hERG gene encodes a K^+ channel that contributes to cardiac repolarisation and its dysfunction is common in cases of cardiac arrhythmias. CD4C/HIV transgenic mice were found to display delayed ventricular repolarization [37] and HIV-1 Tat and Nef are implicated in this process since HIV-Tat was shown to inhibit hERG channel surface expression [38], whilst HIV-1 Nef was found to directly inhibit hERG channel activity when co-expressed in Xenopus oocytes[39]. It is therefore reasonable to speculate that HIV-hERG interactions directly contribute to the prolonged cardiac repolarisation phenotype observed in HIV/AIDS patients.

Other cardiac ion channel-virus interactions of note include Coxsackievirus B3 virus (CVB3), which alters the cellular distribution of L-type Ca^{2+} channels, hERG1 channels and KvLQT1 channels during infection [40]. In mice, CVB3 was also shown to replicate to higher titres in the hearts of mutant animals deficient in the Kir6.1 subunit of K_{ATP} channels, suggesting that K_{ATP} channel deregulation has a critical impact on innate anti-viral immunity in the heart. CVB3-mediated ion channel alterations appear a requirement for virus persistence and may contribute to the arrhythmia frequently observed in CVB3 patients [40], [41].

Virus-mediated respiratory disease

The rate of Na^+ absorption and Cl^- secretion controls the thickness of the fluid layer covering the respiratory surfaces [4], [42]. High throughput compound screens showed that the Na^+ channel opener SDZ-201106 significantly inhibited influenza A virus (IFVA) replication [43], whilst Kunzelmann et al (2000) demonstrated that the amiloride-sensitive epithelial Na^+ channel (ENaC is the main entry mechanism of Na^+ into lung epithelial cells) was inhibited by IFVA [44]. This inhibition was mediated through IFVA-hemagglutinin (HA) activation of phospholipase C and protein kinase C [44], [45]. Additionally, the IFVA viroporin M2 was found to decrease ENaC plasma membrane abundance and associated currents [46]. IFVA-M2 was shown to downregulate the cystic fibrosis transmembrane conductance regulator (CFTR) that conducts Cl^- and thiocyanate ions across epithelial cell membranes [47]. Interestingly a close link between ENaC and CFTR currents has been reported, whereby ENaC activity is dependent upon CFTR function [48], therefore IFVA may employ multiple mechanisms to inhibit ENaC currents. During long-term IFVA infection (>48 hrs) the IFVA multifunctional NS1 protein was shown to activate non-selective cation conductance's that increased Cl^- secretion [49]. This IFVA-mediated modulation of channel function would alter Na^+ and Cl^- ion balance ultimately having detrimental consequences for epithelial fluid clearance, perhaps explaining the progressive disease symptoms associated with IFVA infection.

As with IFVA, severe acute respiratory syndrome coronavirus (SARS-CoV) S and E proteins significantly decrease ENaC protein expression and hence reduce channel activity [50]. PKC inhibition partially increased ENaC currents in SARS-CoV infected cells, indicating a shared mechanism of inhibition with IFVA [50]. A model parainfluenza virus, Sendai virus, was found to promote Cl^- secretion and Na^+ absorption, however unlike IFVA this did not involve PKC activation [42]. Human respiratory syncytial virus (RSV) is also associated with altered ion transport and a reduction in fluid clearance, leading to a range of respiratory tract-associated illnesses. RSV infection favours the mechanism utilised by IFVA, rather than parainfluenza virus, activating PKC to inhibit

ENaC surface expression [42]. An increase in inducible nitric-oxide synthase (iNOS) was noted during infection and subsequent iNOS inhibition led to a recovery of ENaC currents, suggesting a secondary mechanism of channel modulation [51]. Additionally, airway inflammation is mediated by inflammasome activation, an effect at least in part mediated by K^+ channel activation during RSV infection [52].

CONCLUSIONS

Host cell ion channels represent an exciting and emerging field of virus-host interactions and many examples exist in the literature. The role of these channels in viral lifecycles is broad; many viruses utilise ion channel functionality to manipulate entry steps and persistence in infected cells, whilst others alter ion channel currents for as yet unknown viral processes. It is clear that this field is in its infancy and the ability of multiple viruses to alter channel activity will most likely emerge. There are numerous licenced pharmacological agents that target ion channels and modify their activity in disease treatment. Improving our understanding of the role of ion channels during virus pathogenesis will inform us of the potential of ion channel drugs as a new, pharmacologically safe and broad ranging anti-viral therapeutic strategy.

Figure legends

Figure 1. Known virus-ion channel interactions. Phylogenetic tree adapted from Yu et al [2005]) demonstrating the diversity of ion-channel virus interactions from the literature. K^+ channels (*purple*) include voltage-gated (K_v), calcium-activated (K_{Ca}), two-pore (K_{2P}) and inwardly-rectifying (K_{ir}) channel subfamilies. Voltage-gated Ca^{2+} (*green*) and Na^+ (*red*) channels are indicated alongside the cation specific transient-receptor potential (TRP, ligand-gated) subfamilies (*blue*) and two-pore channels (TPC) (*blue*). Additionally represented are the cyclic nucleotide-gated (CNG, ligand gated) and the hyperpolarization-activated cyclic nucleotide-gated (HCN) cation permeable channels *(pink*). The specific channel members with known links to virus infection are highlighted in red.

Figure 2. Predicted mechanisms of ion channel requirement during virus entry. A) EBOV enters cells via macropinocytosis. During virus transit through early and/or late endosomes, GPs are cleaved by cathepsins. EBOV associates with Neimann-Pick Factor 1 (NPC1) in late endosomes, where NAADP facilitates Ca^{2+} release from endosomes via two-pore Ca^{2+} channels (TPC) 1 and 2. Passage through endosomal compartments is accompanied by a decrease in luminal pH and Ca^{2+} concentration. TPC1/2 function is required for progression of EBOV into late endosomes/lysosomes that lack NPC1. These are the predicted sites of EBOV membrane fusion and viral genome release. **B)** The entry mechanisms for many bunyaviruses are not known, however it is established that the increasingly acidic environment along the endosomal pathway leads to structural changes in Gn and Gc that facilitate RNP release. Activity of one or more members of the K_{2P} channel family is required for an as yet unknown early stage of the bunyavirus lifecycle, most likely endosomal trafficking or fusion events. It is unclear however whether K_{2P} channels on the cell surface or within endosomal compartments are required.

Figure 3. Host cell ion channel inhibition by HIV and HCV proteins. A) Oxidative stress activates p38MAPK and Src, mediating phosphorylation of the Kv2.1, increasing its activity and cellular K^+ efflux. The reduction in intracellular K^+ concentration ($[K^+]^i$) activates caspases 3 & 9 which initiate apoptosis. The HCV protein NS5A directly inhibits Kv2.1 phosphorylation preventing Kv2.1 activity and apoptotic induction. This promotes the survival of HCV infected cells. **B)** Functional host cell TASK-1 channels are predicted to prevent the release of HIV-1 from the plasma membrane. HIV-1 Vpu possesses structural similarity to the first transmembrane domain of TASK-1 and incorporates

into TASK-1 dimers, producing a non-functional channel. This channel inhibition facilitates HIV-1 particle release.

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Figure 1

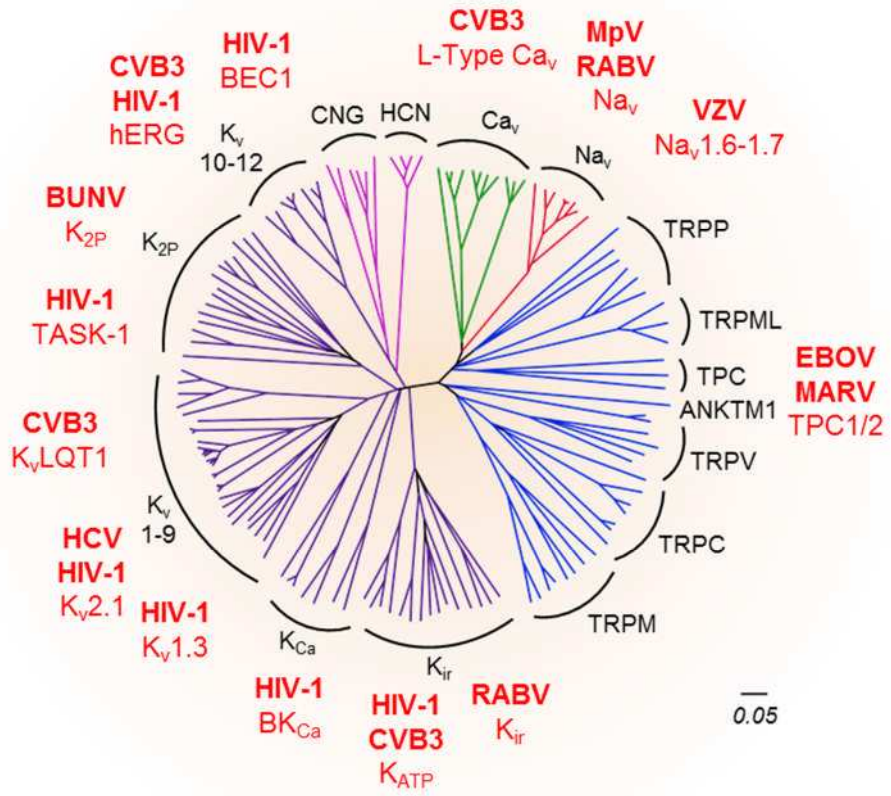
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Figure 2

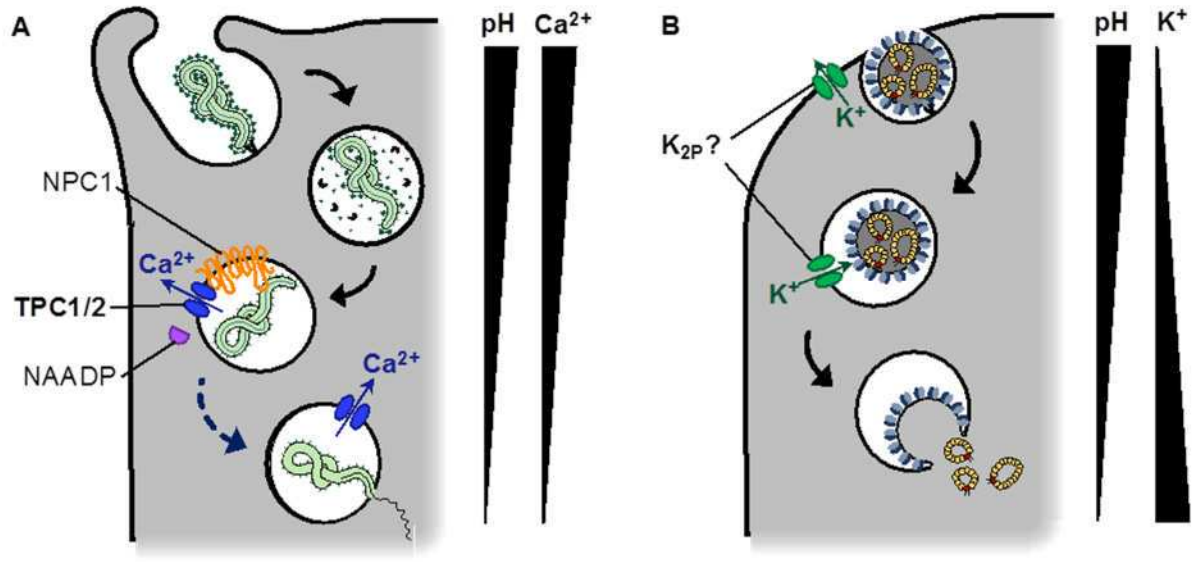
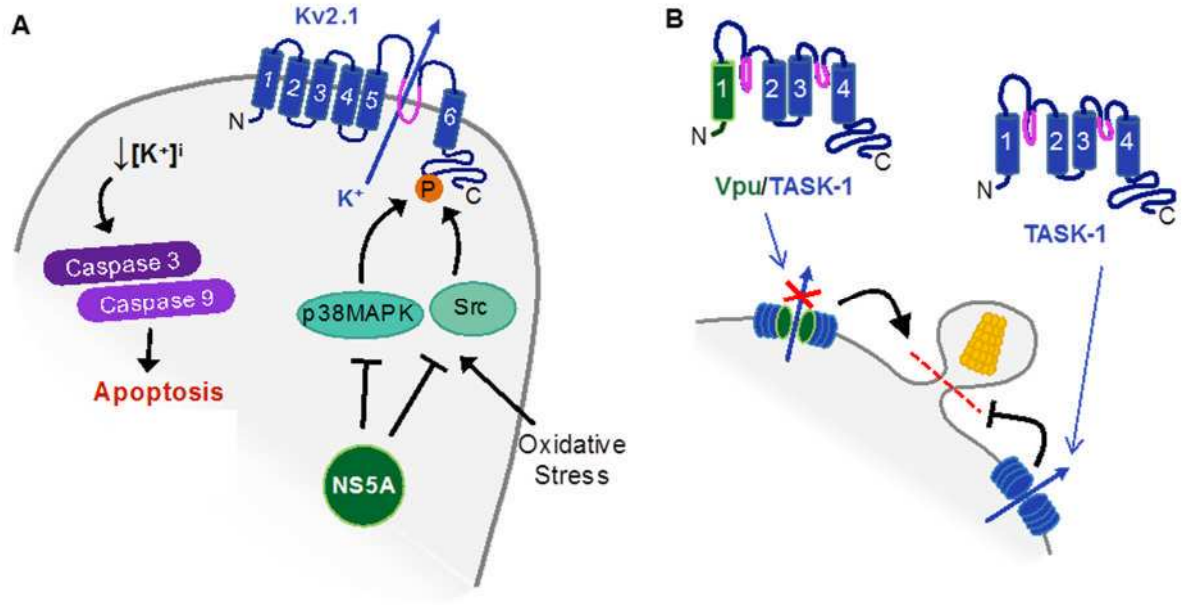


Figure 3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TASK-1