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Review

Ion Channels and Transporters in Inflammation: Special Focus on TRP Channels and TRPC6

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Received: 11 June 2018; Accepted: 29 June 2018; Published: 4 July 2018

Abstract: Allergy and autoimmune diseases are characterised by a multifactorial pathogenic background. Several genes involved in the control of innate and adaptive immunity have been associated with diseases and variably combine with each other as well as with environmental factors and epigenetic processes to shape the characteristics of individual manifestations. Systemic or local perturbations in salt/water balance and in ion exchanges between the intra- and extracellular spaces or among tissues play a role. In this field, usually referred to as elementary immunology, novel evidence has been recently acquired on the role of members of the transient potential receptor (TRP) channel family in several cellular mechanisms of potential significance for the pathophysiology of the immune response. TRP canonical channel 6 (TRPC6) is emerging as a functional element for the control of calcium currents in immune-committed cells and target tissues. In fact, TRPC6 influences leukocytes' tasks such as transendothelial migration, chemotaxis, phagocytosis and cytokine release. TRPC6 also modulates the sensitivity of immune cells to apoptosis and influences tissue susceptibility to ischemia-reperfusion injury and excitotoxicity. Here, we provide a view of the interactions between ion exchanges and inflammation with a focus on the pathogenesis of immune-mediated diseases and potential future therapeutic implications.

Keywords: TRPC6; elementary immunology; inflammation; calcium; sodium; neutrophils; lymphocytes; endothelium; platelets

1. Introduction

Ion exchanges between the intra- and extracellular spaces constitute fundamental mechanisms for the control of cell metabolism and activation state. Changes in the rate of crucial cell reactions such as energy accumulation, protein synthesis and cytoskeleton assembly in response to environmental stimuli are required for the long-term maintenance of homeostasis in complex organisms. Accordingly, genes encoding proteins expressed on the cell membrane to regulate its permeability to ions are crucial for the most complex intra- and intercellular tasks. In particular, ion channels (which account for up to 1% of the human genome [1] and allow the communication among different cells in an organism [1]. The nervous system is important to coordinate the ability of multicellular organisms to sense, adapt,

record and possibly predict external stimuli [2]. The role of ion channels in neuronal activation has been investigated leading to seminal discoveries on their role in physiology and disease.

The current set of human ion channels genes marks the pillars of adaptive immunity [2], suggesting a link between ion channel specialisation and novel biological functions committed to host defence. Consistently, growing evidence is accumulating on the ability of ions, ion channels and transporters and their pharmacological modulators to influence the behaviour of the immune system at the cellular and clinical level, a phenomenon also known as elementary immunology [3].

Transient receptor potential (TRP) channels comprise a wide family of membrane proteins behaving as sodium/calcium permeable molecules. Their role in the deployment of the innate and adaptive immune response has received growing attention [4]. In this setting, TRP canonical channel 6 (TRPC6) has emerged as a modulator of calcium homeostasis in leukocytes and tissues involved by the inflammatory response. Here, we will review the potential mechanisms related to TRPC6 function considering its similarities and interactions with the elements of the cellular machinery committed to ion balance control.

2. Elementary Immunology: An Expanding Landscape

Ion channels and transporters affect immune responses [5] mainly by trimming endosomal pH [6–9] and intracellular calcium concentrations [3,10,11] (Table 1, Figure 1). This latter mechanism involves the intrinsic biophysical properties of a given ion channels or transporter and its ability to allow or facilitate the passage of calcium through the cell membrane. Changes in permeability of calcium channels or transporters can be triggered by either engagement of specific ligands (receptor-operated calcium entry, ROCE), feedforward responses to the release of calcium from intracellular stores (store-operated calcium entry, SOCE) and/or changes in cell polarisation (voltage-operated calcium entry, VOCE) and in the strength of the sodium driving force.

In the majority of cells, the most significant contribution to the rise of intracellular calcium concentrations is due to SOCE events [12–15], which are primed by the release of intracellular calcium stores downstream cell-specific activation pathways. These latter include the B- and T-cell receptor (BcR and TcR) or the Fc receptors pathways [15,16]. The main player in this setting is constituted by a functional triad comprising (a) an inositol-1,4,5-triphosphate (IP_3) receptor channel expressed on the endoplasmic reticulum, which allows calcium to flow into the cytoplasm; (b) a set of cytoplasmic sensors called stromal interaction molecules (STIM); and (c) a membrane channel, bound to STIMs and composed of homo- or heteromers of members of the ORAI channel family [17,18]. The combination of ORAI and STIM protein is usually referred to as the calcium release-activated calcium channel (CRAC). The generation of IP_3 is due to the activity of several types of phospholipases and is paired with the production of diacylglycerol (DAG), which in turn constitutes a ligand for several receptor/channels [19,20]. Intracellular phospholipases are involved in the signal cascades downstream BcR or TcR and can be modulated by the activity of ancillary ion-pathways such as those involving magnesium or zinc interchanges between the intra and extracellular space [21–26]. Auto- or paracrine adenosine triphosphate (ATP), adenosine diphosphate ribose (ADPR), and multiple other chemical ligands or physical stimuli modulate ROCE [27–30].

Voltage-gated calcium channels (Ca_v) are required for leukocyte survival and are thought to be responsive to variations in cell polarisation [31]. Among the Ca_v subtypes, those belonging to the α1 pore-forming subunit family have been identified in lymphocytes [32]. Indirect pharmacological evidence suggests a role of Ca_v in myeloid-derived cells [31]. Sodium–calcium exchangers exploit gradients provided by the sodium-potassium ATPases to extrude calcium from the intracellular space. However, sodium depletion and prolonged cell depolarisation promote calcium entry through these transporters and favour cell activation [33,34].

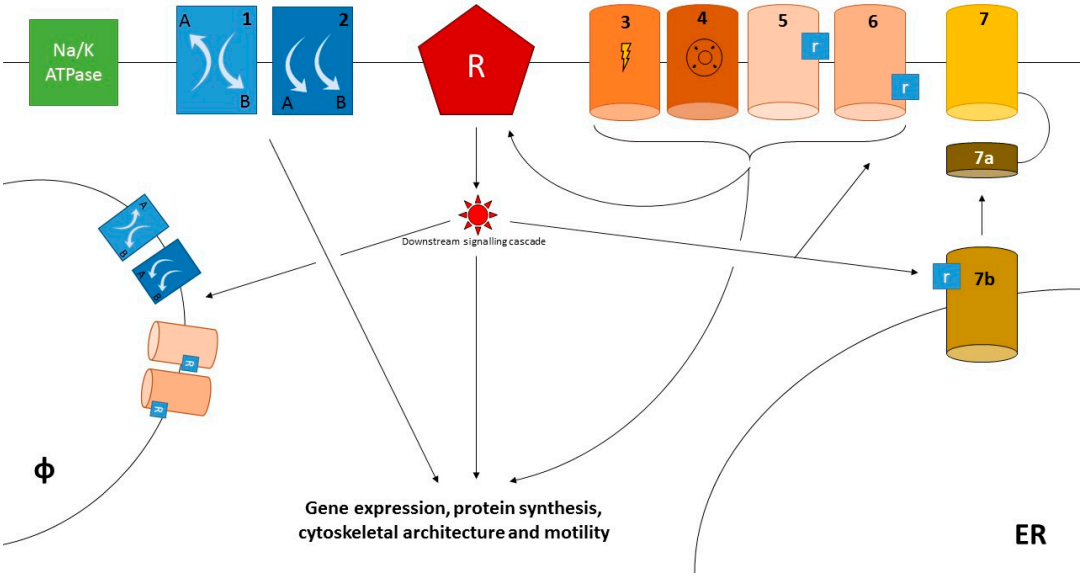

Figure 1. Ion channels and transporters. Ion channels and transporters may affect the behaviour of innate and adaptive immune cells at several levels. Under resting conditions, ion gradients between the intra- and extracellular space are actively generated through the Na/K ATPases. These gradients are exploited by transporters (1, 2) to trim the concentrations of other ions, including calcium. Cell activation after engagement of a cell-specific receptor (R), e.g., the BcR or TcR for lymphocytes or the FcR for myeloid cells, promotes the deployment of downstream signalling cascades that ultimately affect gene expression, protein synthesis and cause cytoskeletal remodelling, enabling cells to perform effector tasks such as chemotaxis, phagocytosis and release of antimicrobial moieties or cytokines. Activation of surface ion channels is integral to these events. A first set of ion channels are activated by physical or biochemical stimuli such as voltage (3), intracellular osmotic pressure (4) or engagement of extracellular (5) or intracellular (6) ligands, which in turn may be directly or indirectly induced by the activation of cell-specific receptors. Conversely, ion currents generated by voltage-operated or receptor-operated channels can exert feedback or feedforward effects on cell activating receptors. Specifically, raised calcium concentrations play a prominent role in mediating cell activation. However, to this regard store-operated calcium entry (SOCE, 7) generally provides a more significant contribution compared to voltage-operated or receptor-operated calcium entry (VOCE, ROCE). SOCE is propitiated by the activation of a inositol-1,4,5-triphosphate (IP_3) receptor channel on the surface of the endoplasmic reticulum (ER, 7b). Increased intracellular IP_3 concentrations are part of the changes induced by cell activation downstream cell-specific receptors (R). The release of calcium from ER stores is then sensed by adaptor proteins such as stromal interaction molecules (STIM; 7a), which in turn activate surface receptors (7), such as those of the ORAI family. Beside the cell surface, ion channels and transporters can also be expressed on intracellular compartments such as the phagolysosomes (ϕ). In this setting, they trim the endosomal pH, thus favouring the digestion of microbes and/or other dangerous moieties.

Gain of function mutations in the sodium–calcium exchanger 1 (*NCX1*) gene, highly expressed at the level of arterial smooth muscle cells, which show a constitutionally slow recovery from depolarisation, associate with arterial hypertension, especially in the setting of sodium overload [35,36]. Enhanced activation and pro-inflammatory differentiation of macrophages and T-lymphocytes and enhanced formation of neutrophil extracellular traps occur in sodium-enriched extracellular environments [37–42]. *NCX1* risk alleles for salt-sensitive hypertension influences the course of nephritis in patients with systemic lupus erythematosus (SLE) [43]. While sodium overload can prompt NCX1 overactivity and enhanced cell activation, sodium-depleting conditions can also promote NCX1-mediated calcium responses and induce TNFalpha release from macrophages, mimicking lipopolysaccharide stimulation [44], and accelerate neutrophil recovery from an activation boost by

increasing the speed of replenishment of intracellular calcium stores [11]. Voltage-gated potassium or sodium channels such as $K_v1.3$ and $Na_v1.5$, calcium-activated potassium channels such as $K_{Ca}3.1$ and chloride channels, all play significant roles in the modulation of membrane polarisation, respectively, favouring or limiting calcium currents [27,45–49]. Macrophages from patients with cystic fibrosis, who have dysfunctional chloride currents due to mutations in the Cystic Fibrosis Transmembrane Conductance Regulator (*CFTR*) gene, are characterised by persistent pro-inflammatory activation and defective phagocytosis, facilitating chronic infection [50,51]. Ion channels and transporters also selectively exert a specifying modulatory role on geographically distinct compartments within immune-committed cells [52].

Besides the modulation of calcium currents, ion channels and transporters involved in the modulation of protons, sodium and calcium influence the functionality of immune cells by regulating the generation of reactive oxygen species (ROS) and interfering with the signalling pathways involved in the processing of immune stimuli [53,54]. Sodium-based transporters are fundamental for the modulation of energy uptake, which ultimately affect the cell lifespan [55]. Immune cells alternatively exploit ion channels and transporters to regulate the unconventional release of cytokines such IL-1β [29,56,57] or modulate their expression by modifying ion balances within the cell nucleus [58,59].

The variety of biochemical effects of ion channels and transporters on cell homeostasis ultimately influences the processing of immune stimuli [15]. Persistent alterations in the control of ion exchanges at the cellular level might ultimately contribute to hypersensitivity and autoimmunity while altered function of ion channels and transporters might influence the ability of target tissues to cope with inflammation-induced damage.

Table 1. Functional impact of selected ion channels and transporters on inflammation.

1. Modulation of Calcium Currents					
1.1 Through Direct Involvement in Calcium Influx/Efflux					
1.1.1 SOCE					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
ORAI1	Ca^{2+}	Neutrophils, Lymphocytes	*Neutrophils*: proliferation, degranulation, cytokines production, cell polarization, migrational guidance with LFA1. *Lymphocytes*: B, T and NK cell proliferation, cytokine production and/or cytotoxicity in vitro; immunity to infection, T cell-mediated autoimmunity and inflammation, and allogeneic T cell responses in vivo; Treg cell development	CRAC channelopathywith immunodeficiency, autoimmunity, lymphoproliferation, muscular hypotonia and ectodermal dysplasia caused by mutations in STIM1 and ORAI1	[10,27,60,61]
ORAI2/3	Ca^{2+}	Neutrophils, Lymphocytes	Cell proliferation, Cytokines production	ND	
STIM1	NA	Neutrophils, Lymphocytes, DC, mast cells	*Neutrophils:* phagocytosis and ROS production *Lymphocytes:* cytokine production in T and B cells, Treg functionality *Mast cells*: FcεR-triggered SOCE	ND	[13,14,27,62–64]
STIM2	NA			Mice deficient of STIM1/2 develop a lymphoproliferative disorder because of dysfunction of Treg cells.	
IP3Rs	Ca^{2+}	All cells	Physiological development of B and T cells	ND	[16–19]
TRPC1	Ca^{2+}, Na^{+}	Endothelium	Enhanced vascular permeability after TNF/thrombin stimulation	ND	[65–67]
TRPC6	Ca^{2+}, Na^{+}	Platelets	Dense granules secretion after thrombin stimulation	ND	[68]
1.1.2 ROCE					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
TRPM2	Ca^{2+}, Na^{+}	Neutrophils, lymphocytes, macrophages and DC	*Neutrophils*: increased activation and endothelial adhesion *Lymphocytes*: T cell proliferation and cytokine secretion *Macrophages and dendritic cells*: regulation of ROS formation	Mice lacking TRPM2 have milder ischaemia-reperfusion injury after myocardial infarction and attenuated experimental brain inflammation	[54,69–75]
TRPC3	Ca^{2+}, Na^{+}	Lymphocytes, macrophages	*Lymphocytes*: T cell activation downstream the TCR *Macrophages*: enhanced pro-inflammatory activation	Mice: accelerated atherosclerosis	[76–78]
TRPC6	Ca^{2+}, Na^{+}	Lymphocytes, neutrophils, endothelium, platelets	*Lymphocytes:* T cell activation *Neutrophils*: chemotaxis, *Endothelium*: enhanced endothelial permeability and activation *Platelets*: TXA2-dependent expression of glycoproteins IIb-IIIa and P-selectin, release of platelet dense granules	Mice: TRPC6 ko associates with milder airway hypersensitivity in asthma models Humans: single study suggesting an association between a TRPC6 polymorphism and neuropsychiatric SLE	[79–85]

Table 1. *Cont.*

TRPV4	Ca^{2+}, Na^{+}	Macrophages	Cell activation after lung barotrauma.	Mice: exacerbated lung inflammation in acute lung injury and increased inflammatory hyperalgesia	[30]
$P2X_1R$, $P2X_4R$	Ca^{2+}, Na^{+}	Lymphocytes, neutrophils, eosinophils, monocytes/macrophages, mast cells, and DC	*Lymphocytes*: T cell proliferation; cytokine production; thymocyte apoptosis *Macrophages*: PGE_2 release, inflammasome activation	ND	[86,87]
$P2X_7R$	Ca^{2+}, Na^{+}, other cations		*Lymphocytes*: T cell survival and cytokine production (downstream the TCR); T cell differentiation into Th17 vs. Treg *Macrophages*: activation of the NLRP3 inflammasome *Mast cells, eosinophils, DC*: inflammatory activation	Mice lacking $P2X_7R$ have attenuated allergic airway response, graft vs. host disease, allograft rejection	[88–90]
1.1.3 VOCE					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
$Ca_v1.1$-4	Ca^{2+}	Lymphocytes	T cell survival, differentiation and progression to effector function	ND	[31,32]
1.1.4 Direct calcium entry following upregulation					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
TRPC3	Ca^{2+}, Na^{+}	Macrophages/microglia	Regulation of cellular activation	Mice: reduced brain inflammation and post-ischaemic myocardial damage	[28,91,92]
TRPC5	Ca^{2+}, Na^{+}	Lymphocytes	Inhibition of Teff activation by Treg	Mice: protection from experimental arthritis	[93,94]
TRPV1	Ca^{2+}, Na^{+}	T lymphocytes	Cell activation (by associating to TCR)	ND	[95]
TRPV2	Ca^{2+}, Na^{+}	Macrophages	Phagocytosis, chemotaxis, following FCγR activation	Mice: TRPV2 deletion prompts accelerated mortality in bacterial infections Humans: cystic Fibrosis macrophages exhibit a defect in TRPV2-mediated calcium influx	[51,96]
TRPV5,6	Ca^{2+}, Na^{+}	Lymphocytes	Cell activation and proliferation (the channels are constitutively active and regulated by endocytosis or at gene expression level).	ND	[97]
1.2 Through intracellular second messengers					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
TRPM7	Mg^{2+}, Ca^{2+}	Lymphocytes, macrophages, mast cells	Lymphocytes: activation downstream BCR and TCR; thymocyte development; production of thymocyte growth factor Macrophages: survival and M2 polarisation Mast cells: survival and activation	ND	[98–103]

Table 1. *Cont.*

MAGT1	Mg^{2+}	Lymphocytes	CD4+ T cell development and activation; immunity to EBV	XMEN syndrome (X-linked mutations in MAGT1)	[104]
ZIP6	Zn^{2+}	T cells, DC	*T cells*: sustained calcium currents enhancing TCR-related pathways and promoting T cell activation DC: inhibition of maturation for antigen presentation	Genetically determined zinc deficit (mutated ZIP4 in the intestinal mucosa) causes acrodermatitis enteropathica with immunodeficiency	[26]
ZIP8		T cells	Sustained calcium currents enhancing TCR-related pathways and promoting T cell activation		
1.3 Through alterations of cell polarisation					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
NCX1	Ca^{2+}, Na^{+}	NeutrophilsMacrophages	Neutrophils: recovery from activation Macrophages: activation, cytokine (TNF) secretion	A single association study suggests potential links among NCX polymorphisms and SLE phenotypes (including severe nephritis)	[11,43,44]
NKCC2	Na^{+}, K^{+}, $2Cl^{-}$	Lymphocytes	Adaptation to extracellular hypertonicity, which eventually leads to the activation of the p38/MAPK → NFAT5 → SGK pathway, which favours Th17 differentiation	ND	[37]
ENaC	Na^{+}				
NHE1	Na^{+}, H^{+}				
TRPM4	Na^{+}, Ca^{2+}	Lymphocytes, macrophages and DC, mast cells	*Lymphocytes:* T helper motility and cytokine production (IL2, IL4, and IFNγ). *Macrophages*: phagocytosis and cytokine release *DC*: motility *Mast cells*: regulation of cell activation	Mice: lack of TRPM4 associates with reduced survival in sepsis and more intense anaphylaxis	[105–108]
$GABA_A$-R	Cl^{-}	Lymphocytes, macrophages and DC, neutrophils	Inhibition of cell activation	In preclinical models GABAergic drugs, protects against type 1 diabetes (T1D), experimental autoimmune encephalomyelitis (EAE), collagen-induced arthritis (CIA), contact dermatitis and allergic asthma. Treatment with gabapentin and pregabalin improved psoriasis (case report).	[49]
CFTR	Cl^{-}	Lymphocytes, macrophages	*Lymphocytes*: modulation of cytokine secretory profile (IL5, IL10) in T cells *Macrophages*: cytokine release, phagocytosis	Cystic fibrosis	[51,109]
$K_v1.3$	K^{+}	Lymphocytes	Enhanced activation of the NLRP3 inflammasome and of IL1β production. Enhanced cell survival and prolonged activation.	A single phase Ib study on dalazatide (a specific $K_v1.3$ inhibitor) shows promise. Applications in SLE have been proposed.	[110–112]

Table 1. *Cont.*

KCa3.1	K^+	Lymphocytes, macrophages, endothelium	*Lymphocytes*: sustained TCR-induced calcium currents to support long-lasting effector functions. *Macrophages*: activation, chemotaxis, infiltration of atherosclerotic plaques *Endothelium*: proliferation	Encouraging evidence of efficacy of K_{Ca}3.1blockers in several models of inflammatory vasculopathy and autoimmunity.	[47,113–116]
Na_v1.5 (SCN5A)	Na^+	T cells	Positive selection of thymocytes	ND	[46]
$P2X_7R$	Ca^{2+}, Na^+ and other cations	Macrophages	Cell death for prolonged depolarisation in case of sustained receptor ligation.	ND	[117]
1.4 Through alterations in the geographical distribution of intracellular calcium					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
TRPC1	Ca^{2+}, Na^+	Neutrophils	Cell polarisation for chemotaxis	ND	[65–67]
2. Modulation of intracellular pH and production of reactive oxygen species					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
TRPM2	Ca^{2+}, Na^+	Macrophages and DC	*Macrophages and DC*: regulation of ROS formation, phagocytosis and bacterial killing	ND	[71,75]
H_v1/VSOP	H^+	lymphocytes, granulocytes, macrophages and DC	All cells: phagocytosis and ROS production B cells: BCR signalling	Mice: loss of the receptor prompts impaired killing of phagocytosed bacteria, ROS production and migration by leukocytes and impaired antibody responses.	[15,53]
NCX	Ca^{2+}, Na^+	DC	Activation of NADPH oxidase and polarisation towards pro-inflammatory DC.		[42]
ENac	Na^+				
NHE	Na^+, H^+				
3. Modulation of endosomal pH					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
TRPC6	Ca^{2+}, Na^+	Macrophages	Phagocytosis and bacterial killing	ND	[8]
TRPM2	Ca^{2+}, Na^+	Macrophages and DC	Phagocytosis and bacterial killing	ND	[71,75]
Proton ATPases	H^+	Macrophages	Phagocytosis and bacterial killing	ND	[118]
Na_v1.5 (SCN5A)	Na^+	Macrophages	endosomal acidification and phagocytosis. Possible polarisation towards an antinflammatory phenotype	Mice: enhanced recovery from EAE.	[45,119]
CLIC 1	Cl^-	Macrophages and DC	Phagocytosis, antigen processing and presentation.	ND	[9,120]

Table 1. *Cont.*

4. Modulation of other intracellular signalling pathways					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
TRPC1	Ca^{2+}, Na^{+}	Macrophages, Mast cells	*Macrophages*: inhibition of IL1β through other ion channels and transporters *Mast-cells*: inhibition of calcium-dependent release of TNF in the late phase of cell activation	Mice: delayed recovery from anaphylaxis	[77,121]
5. Other effects					
Channel	*Permeability*	*Expression (immune cells)*	*Biological effects*	*Clinical correlates*	*Ref.*
SLC5A11	Na^{+}, glucose	Leukocytes (low)	Leukocytes: control of cell osmolarity under hypernatriemic environment, energy uptake, TNF-dependent apoptosis	Polymorphisms associated with susceptibility to SLE	[55,122]
CLIC 1	Cl^{-}	Macrophages	Modulation of cytokine gene expression and processing (conflicting results)	ND	[9,58,59]
CLIC 4	Cl^{-}				

Abbreviations. Ca_v: voltage-gated calcium channels; CFTR: cystic fibrosis transmembrane conductance regulator; CLIC: chloride intracellular channels; DC: dendritic cells; EAE: experimental allergic encephalomyelitis; ENaC: epithelial sodium channel; $GABA_A$-R: gamma-aminobutyric acid receptor type A; NADPH: nicotinamide adenine dinucleotide phosphate; NCX1: sodium-calcium exchanger 1; ND: not determined; NHE1: sodium-hydrogen exchanger 1; NKCC2: sodium-potassium-2 chloride exchanger; PGE2: prostaglandin E2; ROCE: receptor-operated calcium entry; SLC5A11: sodium glucose cotransporter; SOCE: store-operated calcium entry; STIM: stromal interaction molecule; TCR, T cell receptor; TRP: transient receptor potential channel; TXA2: thromboxane A2; VOCE: voltage-operated calcium entry; VSOP: voltage-sensing domain only protein; XMEN, X-linked immunodeficiency with Mg^{2+} defect and EBV infection and neoplasia; ZIP: zinc-regulated transporter (ZRT)/iron regulated transporter(IRT)-like protein.

3. Multiple Roles for Members of the TRP Channel Family in Inflammation

TRP channels are widely expressed and contribute to the control of cell homeostasis. Thus, variations in the functionality of TRP might influence the physiological deployment of the immune response [4,123,124] (Table 1). Six subgroups within the TRP family have been described in humans according to structural homology between members: canonical (i.e., more similar to the original set of channels isolated in *Drosophila* [125], TRPC), vanilloid (TRPV), analogues of melastatin-1 receptor (TRPM), mucolipins (TRPML), polycystins (TRPP), endowed with ankyrin repeats (TRPA). The TRPN subclass owes its name to the NO-mechano-potential C receptor of the worm *Caenorhabditis elegans*. No members of this subclass have been identified in humans, with fishes being the only vertebrates in which this TRP subclass appears to be expressed [123,126].

TRPC channels play a major role in the modulation of calcium currents. In this setting, the formation of heteromeric complexes between different TRPC monomers might extend the spectrum of potential effects of this subclass of TRP channels on calcium homeostasis. In particular, TRPC1, has been proposed as a prototypic biochemical regulator for other membrane receptors thanks to its supposed ability to form heteromers [127–130]. TRPC1 might thus affect the activity of the ORAI/STIM complex as well as of other TRPC, such as TRPC6, to regulate SOCE. However, the evidence supporting this hypothesis is controversial due to the lack of highly specific anti-TRPC1 antibodies and to the need of tissue-restricted models of ORAI/STIM knockout (complete ORAI/STIM deficit is lethal at the embryonic stage in mice) [127]. TRPC1 is highly expressed in the endothelium, where it enhances vascular permeability after TNF/thrombin stimulation [65–67]. The potential ability of TRPC1 to orchestrate the function of other calcium channels is crucial for the maintenance of an intracellular calcium gradient for neutrophil chemotaxis in experimental models [52]. Animal models also suggest that TRPC1 plays a role in the control of IL1β release from macrophages [57]. Similarly, TRPC1 might affect the late effects of anaphylaxis by controlling TNF release from mast cells [121].

TRP channels play an even more relevant role as receptor-operated channels. TRPM2 and TRPC3 are expressed in a wide range of immune cells, including macrophages and lymphocytes, and play a role in T-cell activation after TcR engagement [69,70,76]. TRPM2 is responsible for a significant fraction of calcium currents within endothelial cells and neutrophils [71]. Accordingly, mice lacking TRPM2 show reduced neutrophil infiltrate and less extensive damage following myocardial infarction [72,73]. The main ligand of TRPM2 is ADPR, which lies downstream an intracellular stress-response pathway to ROS. ADPR-mediated activation of TRPM2, in turn, promotes the final step of a regulatory feedback loop that leads to the inhibition of NADPH-oxidase. This process is crucial in macrophages to control the extent of oxidative stress generation during the inflammatory response [54,74]. In this setting, lysosomal expression of TRPM2 is also required for phagocytosis [71,75]. In contrast to the anti-inflammatory effects of TRPM2 on macrophage activity, the role of TRPC3 on macrophage-driven inflammation is less clear. TRPC3 can be activated by DAG and is thought to contribute to vascular inflammation [77,78]. On the other hand, upregulation of TRPC3 downstream the pathway of brain-derived neurotrophic factor might have a protective role against neuronal inflammation and myocardial injury [28,91,92].

TRPV1 contributes to T cell activation by associating to TCR and responding to its engagement with increased calcium flux towards the intracellular space [95], whereas TRPV2 is upregulated by FCγR activation in macrophages and is involved in the deployment of phagocytosis and chemotaxis [96]. A recent study suggests that clustering of TRPV2 in lipid rafts is crucial for bacterial phagocytosis and is defective in patients with cystic fibrosis [51]. TRPM7 has also a crucial role in macrophage activation and is required for the physiological development of functional B- and T cells. Similar to the role of MagT1 receptor in T cells, TRPM7 responds to variation in Mg^{2+} concentrations (itself being more permeable to Mg^{2+} than to Ca^{2+}) and enhances phospholipase activity downstream the BCR/TCR [98,99]. In addition, TRPM7 is crucial for mast cell survival and activation [100,101] as well as for macrophage survival and alternative activation [102]. TRPM7 might work by sensitising leukocytes to relatively low Mg^{2+} levels, rather than responding to acute variations in the concentration

of the cation [103]. This is consistent with the evidence of lon8g-term, rather than sudden effects of TRPM7 deletion on leukocytes, with the partial compensatory role of exogenous Mg^{2+} [24] and with the clinical efficacy of $MgSO_4$ in acute allergic reactions.

TRPC5, TRPV5 and TRPV6 have also been proposed to mediate calcium-dependent activation of leukocytes, although their precise pathways of activation have been less clearly defined [93,94,97,131–133]. TRPM4 exerts an inhibitory effect on calcium currents by promoting membrane depolarisation through calcium-induced sodium entry in macrophages and mast cells [105,106]. In addition, thanks to differential expression levels, TRPM4 exhibits distinct regulatory effects in Th1 and Th2 lymphocytes [107].

4. TRPC6 and Immune Responses

TRPC6 is a member of a TRP subgroup with a probable dual role in SOCE and ROCE (Table 1) [20]. The fraction of calcium currents sustained by TRPC6 varies according to the inciting stimulus and to the cell type [134]. Evidence from neoplastic cell lines suggests that TRPC6-related calcium currents are crucial for the survival and activation of a multitude of histotypes [135–140]. The main physiological agonist of the receptor in the setting of ROCE is DAG. Conversely, endocytosis is the main mechanism for regulating TRPC6 function [141]. TRPC6 is expressed in a wide range of cell types, including neutrophils, lymphocytes, platelets and the endothelium (Table 1, Figure 2) [5]. During the acute phase response, TRPC6 plays a crucial role in neutrophil mobilisation as it enhances macrophage inflammatory protein 2 (MIP-2)- and CXCR2-related chemotactic responses by increasing Ca^{2+} concentration within the intracellular space and promoting actin-based cytoskeleton remodelling [79,80].

During trans-endothelial leukocyte migration TRPC6 acts on the endothelial side by mediating the downstream effects of platelet/endothelial cell adhesion molecule (PECAM/CD31) engagement, thus modulating endothelial permissibility [81]. TRPC6 contributes to loosen the endothelial junctions during acute inflammation, enhancing the effects of cellular and humoral immune mediators on target tissues [82,83]. Histamine-induced vascular leakage, which constitutes the core pathogenic mechanism in an acute hypersensitivity response, is also dependent on TRPC6, at least in animal models [142]. Finally, TRPC6 cooperates in lipopolysaccharide-induced endothelial activation after being itself activated by increasing intracellular concentrations of DAG, downstream the activation of Toll-like receptor 4 [143]. TRPC6 expressed on macrophage phagolysosomes is thought to promote their acidification and ultimately favour anti-microbial responses [8]. Chronically stimulated lung macrophages from patients with chronic obstructive pulmonary disease (COPD) express TRPC6 at high levels [144].

Calcium currents within T-lymphocytes are influenced by TRPC6 [145,146]. TRPC6 knockout dampens Th2-driven hypersensitivity responses in sensitised mice after airway allergen re-challenge [147] while sustained inward calcium currents due to TRPC6 may be indispensable for antimicrobial T cell responses during sepsis [148]. Notably, inhibitors of TRPC6 also have protective effects on the development of lymphocyte apoptosis [84]. This finding is in line with observations from others and us on the potential modulatory role of TRPC6 on cell death. TRPC6 influences endothelial apoptosis in an experimental model of atherosclerosis [148] and we observed that polymorphic gene variants of TRPC6 associate with susceptibility to apoptosis of peripheral blood mononuclear cells and diverging responses to the pharmacological inhibition of the channel in patients with SLE [84].

Enhanced apoptosis and unbalanced cell debris production to clearance ratios are fundamental, often calcium-dependent, events in autoimmunity, especially in the setting of SLE [149–152], a systemic autoimmune disease characterised by the production of autoantibodies against cell nuclear components and inflammatory manifestations involving multiple tissues and organs, such as skin and mucosal surfaces, joints, kidneys, serosae, central and peripheral nerves as well as circulating blood cells. TRPC6 gene variants might influence the secretory profile of SLE lymphocytes [84]. Retrospective

clinical data from a well-characterised cohort of patients with SLE suggests the association between TRPC6 genetic polymorphisms and the risk of developing neuropsychiatric manifestations [85].

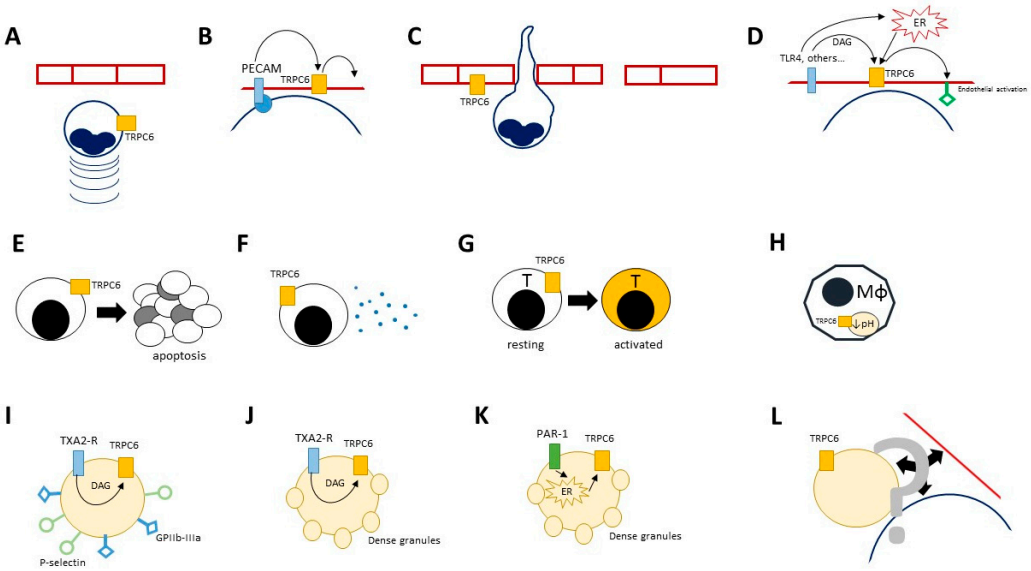

Figure 2. Effects of TRPC6 on immune cells. Activation of TRPC6 plays a critical role in the control of key cellular functions in several immune-committed cells, such as neutrophils (panel (**A**–**D**)), lymphocytes (panel (**E**–**G**)), macrophages (panel (**H**)), platelets (panel (**I**–**L**)) and the endothelium (panel (**A**–**D**,**L**)). TRPC6 contributes to neutrophil activation, adhesion to the vascular walls and extravasation by enhancing the stimulatory effects on chemo-attractants such as MIP-2 and CXCR2 (**A**); by promoting the downstream effects of endothelial cell adhesion molecules such as platelet/endothelial cell adhesion molecule (PECAM; (**B**)) or surface sensors of pro-inflammatory stimuli such as TLR-4 (**D**); by favouring the signal cascades that lead to looser transcellular junction between endothelial cells (**C**). Enhanced TRPC6 activation in lymphocytes might accelerate apoptosis, which could constitute a further trigger for inflammation in autoimmune disorders such as SLE (**E**). The expression of TRPC6 in T cells promotes cytokine release (**F**) and cell activation (**G**), which eventually translate in more aggressive inflammatory or allergic responses. In macrophages, TRPC6 is required for the acidification of endophagolysosomes (**H**). Platelets express high amounts of TRPC6 and might exploit its activation within ROCE (**I**,**J**) or SOCE (**K**) to undergo activation. Receptor-operated stimulation of TRPC6 downstream the thromboxane A2 (TXA2) pathway might be responsible for surface expression of crucial adhesion molecules such as GPIIb-IIIa or P-selectin (**J**) and for the release of platelet dense granules (**J**). This latter event might also occur as the result of TRPC6 activation after mobilisation of calcium from intracellular stores (**K**). Whether these events might impact on the interaction between platelets, leukocytes and the endothelium is still unknown (**L**).

Megakaryocytes and platelets abundantly express TRPC6 on the plasma membrane [153]. TRPC6 promotes calcium entry after being activated by intracellular ligands such as DAG. TRPC6-mediated ROCE in human platelets is restricted to the thromboxane pathway and might induce the expression of surface molecules such as glycoproteins IIb-IIIa or P-selectin and the release of platelet-dense granules. TRPC6 might also be involved in dense granules secretion downstream the thrombin receptors pathway through SOCE [68]. These events play a role in haemostasis and accordingly, prolonged bleeding time and delayed formation of clots have been observed after TRPC6 inhibition or genetic deletion in mice [154,155]. However, evidence from murine models is controversial, as other authors reported normal platelet function and haemostasis in TRPC6 knockout mice [153]. Platelets are part of an interactive network that involves the endothelium and circulating leukocytes and sustains acute and long-term inflammatory responses [156,157]. While evidence has been provided to support a potential

place for TRPC6 as a target for anticoagulation [154], little is known about the impact of TRPC6 inhibition in modulating platelet–leukocyte interactions and related clinical phenotypes [158–161].

5. Effects of TRPC6 Activation and Function on Inflamed Tissues

TRPC6 is a modulator of tissue susceptibility to inflammatory injuries. The channel is expressed in the lungs and is involved in the pathogenesis of ischaemia-reperfusion lung injury [162], septic acute lung injury [143] and idiopathic pulmonary arterial hypertension [163,164]. These events reflect the prominent expression and homeostatic action of TRPC6 on the lung vasculature, in particular at the level of the endothelium and of pulmonary artery smooth muscle cells [163,165]. TRPC6 might also play a role in the biology of other lung-residing cells [136]. Hypoxia-induced elevation of DAG vascular smooth muscle cells promotes ROCE through TRPC6 and subsequent vasoconstriction, which eventually exacerbates ischaemia [166]. Similar vasomotor effects have been demonstrated in aortic smooth muscle cells [167,168] and in the medial layer of coronary arteries in porcine models [169]. In addition, TRPC6-dependent surges in intracellular calcium concentrations contribute to the susceptibility of cardiomyocytes to ischaemia-reperfusion injury [170,171] and to long-term maladaptive responses leading to cardiac remodelling [172,173].

Animal models in which TRPC6 expression had been silenced revealed that TRPC6-mediated cellular responses prevented necroptosis of renal tubular epithelial cells [174], suggesting that TRPC6 contributes to protect the kidney from ischemia-reperfusion injury. Downregulation of TRPC6 influences the ability of mesangial cells to contract following angiotensin II stimulation [175,176] while overactive TRPC6 in podocytes promotes cytoskeletal remodelling due to sustained increased intracellular calcium concentrations with podosome disassembly and eventual proteinuria. Gain of function mutations of TRPC6 have been associated with familial forms of focal segmental glomerular sclerosis [177,178]. TRPC6 inhibition improves protein retention in rat models of nephrosis, suggesting that aberrant TRPC6 function might also exacerbate the clinical picture of patients with acquired forms of glomerular injury [179,180]. Accordingly, higher levels of TRPC6 RNA were found in urines of patients with more aggressive forms of lupus nephritis in a pilot study [181]. More recently, TRPC6 has also been implicated in the pathogenesis of tubular interstitial fibrosis [182].

These latter observations are consistent with the wider role of TRPC6 in sustaining wound healing and tissue remodelling responses after injury. In particular, in line with its role as a promoter of vascular smooth muscle cell contraction, TRPC6 is required for myofibroblast trans-differentiation from resting fibroblasts [183]. Recent evidence suggests the implication of this phenomenon in pulmonary fibrosis [184] and in intestinal strictures in patients with Crohn's disease [185].

TRPC6 is expressed in neuronal tissues. TRPC6 activity in the nervous system seems to contrast the sequelae of brain ischaemia and reperfusion. Neurons are protected from post-ischaemic excitotoxicity by an indirect effect of TRPC6 on NMDA receptors [186,187] while under ischaemic conditions, TRPC6 degradation is enhanced in murine neurons by an IL17-dependent pathway. Inhibition of IL17 or of the downstream proteolytic enzyme calpain restores TRPC6 functions and reduces the area of post-ischemic necrosis [188]. A role for TRPC6 in modulating synaptic plasticity [189,190] and enhancing microglial activation [62] has been proposed.

6. Conclusions

The modulation of salt–water balance and electrolyte exchanges between the intra- and extra-cellular space has effects on the deployment of the immune response. Among the ion channels and transporters concurring to define the shape of the landscape of elementary immunology, TRPC6 seems to play a role in the regulation of several inflammatory events. More robust evidence from controlled human studies is required to pave the way to possible applications of TRPC6 as a target for diagnostic assessment or therapeutic intervention.

Acknowledgments: This work has been supported by grants from the Italian Association for Cancer Research (AIRC), the Cariplo Foundation and the Italian Ministry of Health (Ministero della Salute).

Conflicts of Interest: The authors declare that they have no conflict of interest in connection with this paper.

References

1. Venter, J.C.; Adams, M.D.; Myers, E.W.; Li, P.W.; Mural, R.J.; Sutton, G.G.; Smith, H.O.; Yandell, M.; Evans, C.A.; Holt, R.A.; et al. The sequence of the human genome. *Science* **2001**, *291*, 1304–1351. [CrossRef] [PubMed]
2. Chen, S.; He, F.F.; Wang, H.; Fang, Z.; Shao, N.; Tian, X.J.; Liu, J.S.; Zhu, Z.H.; Wang, Y.M.; Wang, S.; et al. Calcium entry via TRPC6 mediates albumin overload-induced endoplasmic reticulum stress and apoptosis in podocytes. *Cell Calcium* **2011**, *50*, 523–529. [CrossRef] [PubMed]
3. Schatz, V.; Neubert, P.; Schroder, A.; Binger, K.; Gebhard, M.; Muller, D.N.; Luft, F.C.; Titze, J.; Jantsch, J. Elementary immunology: Na(+) as a regulator of immunity. *Pediatr. Nephrol.* **2017**, *32*, 201–210. [CrossRef] [PubMed]
4. Parenti, A.; De Logu, F.; Geppetti, P.; Benemei, S. What is the evidence for the role of TRP channels in inflammatory and immune cells? *Br. J. Pharmacol.* **2016**, *173*, 953–969. [CrossRef] [PubMed]
5. European Bioinformatics Institute (EMBL-EBI); SIB Swiss Institute of Bioinformatics; (PIR), P.I.R. Universal Protein Resource (Uniprot). Available online: http://www.uniprot.org/ (accessed on 5 June 2018).
6. Sumoza-Toledo, A.; Lange, I.; Cortado, H.; Bhagat, H.; Mori, Y.; Fleig, A.; Penner, R.; Partida-Sanchez, S. Dendritic cell maturation and chemotaxis is regulated by TRPM2-mediated lysosomal Ca^{2+} release. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2011**, *25*, 3529–3542. [CrossRef] [PubMed]
7. Maxson, M.E.; Grinstein, S. *The Vacuolar-Type H^+-ATPase at a Glance—More Than a Proton Pump*; The Company of Biologists Ltd.: Cambridge, UK, 2014.
8. Riazanski, V.; Gabdoulkhakova, A.G.; Boynton, L.S.; Eguchi, R.R.; Deriy, L.V.; Hogarth, D.K.; Loaec, N.; Oumata, N.; Galons, H.; Brown, M.E.; et al. TRPC6 channel translocation into phagosomal membrane augments phagosomal function. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, E6486–E6495. [CrossRef] [PubMed]
9. Salao, K.; Jiang, L.; Li, H.; Tsai, V.W.; Husaini, Y.; Curmi, P.M.; Brown, L.J.; Brown, D.A.; Breit, S.N. Clic1 regulates dendritic cell antigen processing and presentation by modulating phagosome acidification and proteolysis. *Biol. Open* **2016**, *5*, 620–630. [CrossRef] [PubMed]
10. Clemens, R.A.; Lowell, C.A. Store-operated calcium signaling in neutrophils. *J. Leukoc. Biol.* **2015**, *98*, 497–502. [CrossRef] [PubMed]
11. Tintinger, G.R.; Steel, H.C.; Theron, A.J.; Anderson, R. Pharmacological control of neutrophil-mediated inflammation: Strategies targeting calcium handling by activated polymorphonuclear leukocytes. *Drug Des. Dev. Ther.* **2009**, *2*, 95–104.
12. Vaeth, M.; Maus, M.; Klein-Hessling, S.; Freinkman, E.; Yang, J.; Eckstein, M.; Cameron, S.; Turvey, S.E.; Serfling, E.; Berberich-Siebelt, F. Store-operated Ca^{2+} entry controls clonal expansion of T cells through metabolic reprogramming. *Immunity* **2017**, *47*, 664–679. [CrossRef] [PubMed]
13. Clemens, R.A.; Chong, J.; Grimes, D.; Hu, Y.; Lowell, C.A. STIM1 and STIM2 cooperatively regulate mouse neutrophil store-operated calcium entry and cytokine production. *Blood* **2017**, *130*, 1565–1577. [CrossRef] [PubMed]
14. Vaeth, M.; Eckstein, M.; Shaw, P.J.; Kozhaya, L.; Yang, J.; Berberich-Siebelt, F.; Clancy, R.; Unutmaz, D.; Feske, S. Store-operated Ca(2+) entry in follicular T cells controls humoral immune responses and autoimmunity. *Immunity* **2016**, *44*, 1350–1364. [CrossRef] [PubMed]
15. Vaeth, M.; Feske, S. Ion channelopathies of the immune system. *Curr. Opin. Immunol.* **2018**, *52*, 39–50. [CrossRef] [PubMed]
16. Harr, M.W.; Rong, Y.; Bootman, M.D.; Roderick, H.L.; Distelhorst, C.W. Glucocorticoid-mediated inhibition of LCK modulates the pattern of T cell receptor-induced calcium signals by down-regulating inositol 1,4,5-trisphosphate receptors. *J. Biol. Chem.* **2009**, *284*, 31860–31871. [CrossRef] [PubMed]
17. Tang, H.; Wang, H.; Lin, Q.; Fan, F.; Zhang, F.; Peng, X.; Fang, X.; Liu, J.; Ouyang, K. Loss of IP3 receptor-mediated Ca(2+) release in mouse B cells results in abnormal B cell development and function. *J. Immunol.* **2017**, *199*, 570–580. [CrossRef] [PubMed]
18. Ouyang, K.; Leandro Gomez-Amaro, R.; Stachura, D.L.; Tang, H.; Peng, X.; Fang, X.; Traver, D.; Evans, S.M.; Chen, J. Loss of IP3R-dependent Ca^{2+} signalling in thymocytes leads to aberrant development and acute lymphoblastic leukemia. *Nat. Commun.* **2014**, *5*, 4814. [CrossRef] [PubMed]

19. Lichtenegger, M.; Tiapko, O.; Svobodova, B.; Stockner, T.; Glasnov, T.N.; Schreibmayer, W.; Platzer, D.; Cruz, G.G.; Krenn, S.; Schober, R. An optically controlled probe identifies lipid-gating fenestrations within the TRPC3 channel. *Nat. Chem. Biol.* **2018**, *14*, 396. [CrossRef] [PubMed]
20. Dietrich, A.; Gudermann, T. TRPC6: Physiological function and pathophysiological relevance. *Handb. Exp. Pharmacol.* **2014**, *222*, 157–188. [PubMed]
21. Li, F.-Y.; Chaigne-Delalande, B.; Kanellopoulou, C.; Davis, J.C.; Matthews, H.F.; Douek, D.C.; Cohen, J.I.; Uzel, G.; Su, H.C.; Lenardo, M.J. Signaling role for Mg^{2+} revealed by immunodeficiency due to loss of MAGT1. *Nature* **2011**, *475*, 471. [CrossRef] [PubMed]
22. Deason-Towne, F.; Perraud, A.-L.; Schmitz, C. Identification of SER/THR phosphorylation sites in the C2-domain of phospholipase c γ2 (plcγ2) using TRPM7-kinase. *Cell. Signal.* **2012**, *24*, 2070–2075. [CrossRef] [PubMed]
23. Cahalan, M.D.; Chandy, K.G. The functional network of ion channels in T lymphocytes. *Immunol. Rev.* **2009**, *231*, 59–87. [CrossRef] [PubMed]
24. Schmitz, C.; Perraud, A.-L.; Johnson, C.O.; Inabe, K.; Smith, M.K.; Penner, R.; Kurosaki, T.; Fleig, A.; Scharenberg, A.M. Regulation of vertebrate cellular Mg^{2+} homeostasis by TRPM7. *Cell* **2003**, *114*, 191–200. [CrossRef]
25. Gotru, S.K.; Gil-Pulido, J.; Beyersdorf, N.; Diefenbach, A.; Becker, I.C.; Vögtle, T.; Remer, K.; Chubanov, V.; Gudermann, T.; Hermanns, H.M. Cutting edge: Imbalanced cation homeostasis in MAGT1-deficient B cells dysregulates B cell development and signaling in mice. *J. Immunol.* **2018**, *200*, 2529–2534. [CrossRef] [PubMed]
26. Hojyo, S.; Fukada, T. Roles of zinc signaling in the immune system. *J. Immunol. Res.* **2016**, *2016*. [CrossRef] [PubMed]
27. Feske, S.; Wulff, H.; Skolnik, E.Y. Ion channels in innate and adaptive immunity. *Annu. Rev. Immunol.* **2015**, *33*, 291–353. [CrossRef] [PubMed]
28. Mizoguchi, Y.; Monji, A. TRPC channels and brain inflammation. In *Transient Receptor Potential Canonical Channels and Brain Diseases*; Springer: Berlin/Heidelberg, Germany, 2017; pp. 111–121.
29. Di Virgilio, F.; Dal Ben, D.; Sarti, A.C.; Giuliani, A.L.; Falzoni, S. The P2X7 receptor in infection and inflammation. *Immunity* **2017**, *47*, 15–31. [CrossRef] [PubMed]
30. Hamanaka, K.; Jian, M.Y.; Townsley, M.I.; King, J.A.; Liedtke, W.; Weber, D.S.; Eyal, F.G.; Clapp, M.M.; Parker, J.C. TRPV4 channels augment macrophage activation and ventilator-induced lung injury. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2010**, *299*, L353–L362. [CrossRef] [PubMed]
31. Davenport, B.; Li, Y.; Heizer, J.W.; Schmitz, C.; Perraud, A.L. Signature channels of excitability no more: L-type channels in immune cells. *Front. Immunol.* **2015**, *6*, 375. [CrossRef] [PubMed]
32. Badou, A.; Jha, M.K.; Matza, D.; Flavell, R.A. Emerging roles of L-type voltage-gated and other calcium channels in T lymphocytes. *Front. Immunol.* **2013**, *4*, 243. [CrossRef] [PubMed]
33. Blaustein, M.P.; Zhang, J.; Chen, L.; Song, H.; Raina, H.; Kinsey, S.P.; Izuka, M.; Iwamoto, T.; Kotlikoff, M.I.; Lingrel, J.B.; et al. The pump, the exchanger, and endogenous Ouabain: Signaling mechanisms that link salt retention to hypertension. *Hypertension* **2009**, *53*, 291–298. [CrossRef] [PubMed]
34. Boscia, F.; D'Avanzo, C.; Pannaccione, A.; Secondo, A.; Casamassa, A.; Formisano, L.; Guida, N.; Scorziello, A.; Di Renzo, G.; Annunziato, L. New roles of NCX in glial cells: Activation of microglia in ischemia and differentiation of oligodendrocytes. *Adv. Exp. Med. Biol.* **2013**, *961*, 307–316. [PubMed]
35. Iwamoto, T.; Kita, S.; Zhang, J.; Blaustein, M.P.; Arai, Y.; Yoshida, S.; Wakimoto, K.; Komuro, I.; Katsuragi, T. Salt-sensitive hypertension is triggered by Ca^{2+} entry via Na^{+}/Ca^{2+} exchanger type-1 in vascular smooth muscle. *Nat. Med.* **2004**, *10*, 1193. [CrossRef] [PubMed]
36. Citterio, L.; Simonini, M.; Zagato, L.; Salvi, E.; Delli Carpini, S.; Lanzani, C.; Messaggio, E.; Casamassima, N.; Frau, F.; D'Avila, F.; et al. Genes involved in vasoconstriction and vasodilation system affect salt-sensitive hypertension. *PLoS ONE* **2011**, *6*, e19620. [CrossRef] [PubMed]
37. Kleinewietfeld, M.; Manzel, A.; Titze, J.; Kvakan, H.; Yosef, N.; Linker, R.A.; Muller, D.N.; Hafler, D.A. Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells. *Nature* **2013**, *496*, 518–522. [CrossRef] [PubMed]
38. Hernandez, A.L.; Kitz, A.; Wu, C.; Lowther, D.E.; Rodriguez, D.M.; Vudattu, N.; Deng, S.; Herold, K.C.; Kuchroo, V.K.; Kleinewietfeld, M.; et al. Sodium chloride inhibits the suppressive function of FOXP3+ regulatory T cells. *J. Clin. Investig.* **2015**, *125*, 4212–4222. [CrossRef] [PubMed]

39. Junger, W.G.; Liu, F.C.; Loomis, W.H.; Hoyt, D.B. Hypertonic saline enhances cellular immune function. *Circ. Shock* **1994**, *42*, 190–196. [PubMed]
40. Binger, K.J.; Gebhardt, M.; Heinig, M.; Rintisch, C.; Schroeder, A.; Neuhofer, W.; Hilgers, K.; Manzel, A.; Schwartz, C.; Kleinewietfeld, M.; et al. High salt reduces the activation of IL-4- and IL-13-stimulated macrophages. *J. Clin. Investig.* **2015**, *125*, 4223–4238. [CrossRef] [PubMed]
41. Shapiro, L.; Dinarello, C.A. Osmotic regulation of cytokine synthesis in vitro. *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 12230–12234. [CrossRef] [PubMed]
42. Barbaro, N.R.; Foss, J.D.; Kryshtal, D.O.; Tsyba, N.; Kumaresan, S.; Xiao, L.; Mernaugh, R.L.; Itani, H.A.; Loperena, R.; Chen, W.; et al. Dendritic cell amiloride-sensitive channels mediate sodium-induced inflammation and hypertension. *Cell Rep.* **2017**, *21*, 1009–1020. [CrossRef] [PubMed]
43. Ramirez, G.A.; Lanzani, C.; Bozzolo, E.P.; Zagato, L.; Citterio, L.; Casamassima, N.; Canti, V.; Sabbadini, M.G.; Rovere-Querini, P.; Manunta, P.; et al. Beta-adducin and sodium-calcium exchanger 1 gene variants are associated with systemic lupus erythematosus and lupus nephritis. *Rheumatol. Int.* **2015**, *35*, 1975–1983. [CrossRef] [PubMed]
44. Staiano, R.I.; Granata, F.; Secondo, A.; Petraroli, A.; Loffredo, S.; Frattini, A.; Annunziato, L.; Marone, G.; Triggiani, M. Expression and function of Na^+/Ca^{2+} exchangers 1 and 3 in human macrophages and monocytes. *Eur. J. Immunol.* **2009**, *39*, 1405–1418. [CrossRef] [PubMed]
45. Carrithers, L.M.; Hulseberg, P.; Sandor, M.; Carrithers, M.D. The human macrophage sodium channel NAV1.5 regulates mycobacteria processing through organelle polarization and localized calcium oscillations. *FEMS Immunol. Med. Microbiol.* **2011**, *63*, 319–327. [CrossRef] [PubMed]
46. Lo, W.L.; Donermeyer, D.L.; Allen, P.M. A voltage-gated sodium channel is essential for the positive selection of Cd4(+) T cells. *Nat. Immunol.* **2012**, *13*, 880–887. [CrossRef] [PubMed]
47. Di, L.; Srivastava, S.; Zhdanova, O.; Ding, Y.; Li, Z.; Wulff, H.; Lafaille, M.; Skolnik, E.Y. Inhibition of the K^+ channel KCa3.1 ameliorates T cell-mediated colitis. *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 1541–1546. [CrossRef] [PubMed]
48. Grimaldi, A.; D'Alessandro, G.; Golia, M.T.; Grossinger, E.M.; Di Angelantonio, S.; Ragozzino, D.; Santoro, A.; Esposito, V.; Wulff, H.; Catalano, M.; et al. KCa3.1 inhibition switches the phenotype of glioma-infiltrating microglia/macrophages. *Cell Death Dis.* **2016**, *7*, e2174. [CrossRef] [PubMed]
49. Prud'homme, G.J.; Glinka, Y.; Wang, Q. Immunological gabaergic interactions and therapeutic applications in autoimmune diseases. *Autoimmun. Rev.* **2015**, *14*, 1048–1056. [CrossRef] [PubMed]
50. Simonin-Le Jeune, K.; Le Jeune, A.; Jouneau, S.; Belleguic, C.; Roux, P.F.; Jaguin, M.; Dimanche-Boitre, M.T.; Lecureur, V.; Leclercq, C.; Desrues, B.; et al. Impaired functions of macrophage from cystic fibrosis patients: Cd11b, TLR-5 decrease and SCD14, inflammatory cytokines increase. *PLoS ONE* **2013**, *8*, e75667. [CrossRef] [PubMed]
51. Leveque, M.; Penna, A.; Le Trionnaire, S.; Belleguic, C.; Desrues, B.; Brinchault, G.; Jouneau, S.; Lagadic-Gossmann, D.; Martin-Chouly, C. Phagocytosis depends on TRPV2-mediated calcium influx and requires TRPV2 in lipids rafts: Alteration in macrophages from patients with cystic fibrosis. *Sci. Rep.* **2018**, *8*, 4310. [CrossRef] [PubMed]
52. Lindemann, O.; Strodthoff, C.; Horstmann, M.; Nielsen, N.; Jung, F.; Schimmelpfennig, S.; Heitzmann, M.; Schwab, A. TRPC1 regulates FMLP-stimulated migration and chemotaxis of neutrophil granulocytes. *Biochim. Biophys. Acta* **2015**, *1853*, 2122–2130. [CrossRef] [PubMed]
53. Capasso, M.; Bhamrah, M.K.; Henley, T.; Boyd, R.S.; Langlais, C.; Cain, K.; Dinsdale, D.; Pulford, K.; Khan, M.; Musset, B. HVCN1 modulates BCR signal strength via regulation of BCR-dependent generation of reactive oxygen species. *Nat. Immunol.* **2010**, *11*, 265. [CrossRef] [PubMed]
54. Di, A.; Gao, X.P.; Qian, F.; Kawamura, T.; Han, J.; Hecquet, C.; Ye, R.D.; Vogel, S.M.; Malik, A.B. The redox-sensitive cation channel TRPM2 modulates phagocyte ROS production and inflammation. *Nat. Immunol.* **2011**, *13*, 29–34. [CrossRef] [PubMed]
55. Tsai, L.J.; Hsiao, S.H.; Tsai, L.M.; Lin, C.Y.; Tsai, J.J.; Liou, D.M.; Lan, J.L. The sodium-dependent glucose cotransporter SLC5A11 as an autoimmune modifier gene in SLE. *Tissue Antigens* **2008**, *71*, 114–126. [CrossRef] [PubMed]
56. Lopez-Castejon, G.; Brough, D. Understanding the mechanism of IL-1β secretion. *Cytokine Growth Factor Rev.* **2011**, *22*, 189–195. [CrossRef] [PubMed]

57. Py, B.F.; Jin, M.; Desai, B.N.; Penumaka, A.; Zhu, H.; Kober, M.; Dietrich, A.; Lipinski, M.M.; Henry, T.; Clapham, D.E. Caspase-11 controls interleukin-1β release through degradation of TRPC1. *Cell Rep.* **2014**, *6*, 1122–1128. [CrossRef] [PubMed]
58. Malik, M.; Jividen, K.; Padmakumar, V.; Cataisson, C.; Li, L.; Lee, J.; Howard, O.Z.; Yuspa, S.H. Inducible NOS-induced chloride intracellular channel 4 (CLIC4) nuclear translocation regulates macrophage deactivation. *Proc. Natl. Acad. Sci. USA* **2012**, *109*, 6130–6135. [CrossRef] [PubMed]
59. Domingo-Fernández, R.; Coll, R.C.; Kearney, J.; Breit, S.; O'Neill, L.A. The intracellular chloride channel proteins CLIC1 and CLIC4 induce IL-1β transcription and activate the NLRP3 inflammasome. *J. Biol. Chem.* **2017**, *292*, 12077–12087. [CrossRef] [PubMed]
60. Hogan, P.G.; Lewis, R.S.; Rao, A. Molecular basis of calcium signaling in lymphocytes: STIM and ORAI. *Annu. Rev. Immunol.* **2010**, *28*, 491–533. [CrossRef] [PubMed]
61. Bogeski, I.; Kummerow, C.; Al-Ansary, D.; Schwarz, E.C.; Koehler, R.; Kozai, D.; Takahashi, N.; Peinelt, C.; Griesemer, D.; Bozem, M. Differential redox regulation of ORAI ion channels: A mechanism to tune cellular calcium signaling. *Sci. Signal.* **2010**, *3*, ra24. [CrossRef] [PubMed]
62. Liu, N.; Zhuang, Y.; Zhou, Z.; Zhao, J.; Chen, Q.; Zheng, J. Nf-kappab dependent up-regulation of TRPC6 by abeta in bv-2 microglia cells increases Cox-2 expression and contributes to hippocampus neuron damage. *Neurosci. Lett.* **2017**, *651*, 1–8. [CrossRef] [PubMed]
63. Desvignes, L.; Weidinger, C.; Shaw, P.; Vaeth, M.; Ribierre, T.; Liu, M.; Fergus, T.; Kozhaya, L.; McVoy, L.; Unutmaz, D.; et al. Stim1 controls T cell-mediated immune regulation and inflammation in chronic infection. *J. Clin. Investig.* **2015**, *125*, 2347–2362. [CrossRef] [PubMed]
64. Nunes-Hasler, P.; Maschalidi, S.; Lippens, C.; Castelbou, C.; Bouvet, S.; Guido, D.; Bermont, F.; Bassoy, E.Y.; Page, N.; Merkler, D.; et al. STIM1 promotes migration, phagosomal maturation and antigen cross-presentation in dendritic cells. *Nat. Commun.* **2017**, *8*, 1852. [CrossRef] [PubMed]
65. Paria, B.C.; Vogel, S.M.; Ahmmed, G.U.; Alamgir, S.; Shroff, J.; Malik, A.B.; Tiruppathi, C. Tumor necrosis factor-alpha-induced TRPC1 expression amplifies store-operated Ca^{2+} influx and endothelial permeability. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2004**, *287*, L1303–L1313. [CrossRef] [PubMed]
66. Tiruppathi, C.; Ahmmed, G.U.; Vogel, S.M.; Malik, A.B. Ca^{2+} signaling, TRP channels, and endothelial permeability. *Microcirculation* **2006**, *13*, 693–708. [CrossRef] [PubMed]
67. Qu, Y.Y.; Wang, L.M.; Zhong, H.; Liu, Y.M.; Tang, N.; Zhu, L.P.; He, F.; Hu, Q.H. TRPC1 stimulates calciumsensing receptorinduced storeoperated Ca^{2+} entry and nitric oxide production in endothelial cells. *Mol. Med. Rep.* **2017**, *16*, 4613–4619. [CrossRef] [PubMed]
68. Lopez, E.; Bermejo, N.; Berna-Erro, A.; Alonso, N.; Salido, G.M.; Redondo, P.C.; Rosado, J.A. Relationship between calcium mobilization and platelet alpha- and delta-granule secretion. A role for TRPC6 in thrombin-evoked delta-granule exocytosis. *Arch. Biochem. Biophys.* **2015**, *585*, 75–81. [CrossRef] [PubMed]
69. Melzer, N.; Hicking, G.; Gobel, K.; Wiendl, H. TRPM2 cation channels modulate T cell effector functions and contribute to autoimmune CNS inflammation. *PLoS ONE* **2012**, *7*, e47617. [CrossRef] [PubMed]
70. Wehrhahn, J.; Kraft, R.; Harteneck, C.; Hauschildt, S. Transient receptor potential melastatin 2 is required for lipopolysaccharide-induced cytokine production in human monocytes. *J. Immunol.* **2010**, *184*, 2386–2393. [CrossRef] [PubMed]
71. Syed Mortadza, S.A.; Wang, L.; Li, D.; Jiang, L.H. TRPM2 channel-mediated ROS-sensitive Ca(2+) signaling mechanisms in immune cells. *Front. Immunol.* **2015**, *6*, 407. [CrossRef] [PubMed]
72. Hiroi, T.; Wajima, T.; Negoro, T.; Ishii, M.; Nakano, Y.; Kiuchi, Y.; Mori, Y.; Shimizu, S. Neutrophil TRPM2 channels are implicated in the exacerbation of myocardial ischaemia/reperfusion injury. *Cardiovasc. Res.* **2013**, *97*, 271–281. [CrossRef] [PubMed]
73. Mittal, M.; Nepal, S.; Tsukasaki, Y.; Hecquet, C.M.; Soni, D.; Rehman, J.; Tiruppathi, C.; Malik, A.B. Neutrophil activation of endothelial cell-expressed TRPM2 mediates transendothelial neutrophil migration and vascular injury. *Circ. Res.* **2017**, *121*, 1081–1091. [CrossRef] [PubMed]
74. Yamamoto, S.; Shimizu, S.; Kiyonaka, S.; Takahashi, N.; Wajima, T.; Hara, Y.; Negoro, T.; Hiroi, T.; Kiuchi, Y.; Okada, T. TRPM2-mediated Ca2+ influx induces chemokine production in monocytes that aggravates inflammatory neutrophil infiltration. *Nat. Med.* **2008**, *14*, 738. [CrossRef] [PubMed]
75. Di, A.; Kiya, T.; Gong, H.; Gao, X.; Malik, A.B. Role of the phagosomal redox-sensitive TRP channel TRPM2 in regulating bactericidal activity of macrophages. *J. Cell Sci.* **2017**, *130*, 735–744. [CrossRef] [PubMed]

76. Philipp, S.; Strauss, B.; Hirnet, D.; Wissenbach, U.; Mery, L.; Flockerzi, V.; Hoth, M. TRPC3 mediates T-cell receptor-dependent calcium entry in human T-lymphocytes. *J. Biol. Chem.* **2003**, *278*, 26629–26638. [CrossRef] [PubMed]
77. Solanki, S.; Dube, P.R.; Birnbaumer, L.; Vazquez, G. Reduced necrosis and content of apoptotic m1 macrophages in advanced atherosclerotic plaques of mice with macrophage-specific loss of TRPC3. *Sci. Rep.* **2017**, *7*, 42526. [CrossRef] [PubMed]
78. Feng, M.; Xu, D.; Wang, L. miR-26a inhibits atherosclerosis progression by targeting TRPC3. *Cell Biosci.* **2018**, *8*, 4. [CrossRef] [PubMed]
79. Damann, N.; Owsianik, G.; Li, S.; Poll, C.; Nilius, B. The calcium-conducting ion channel transient receptor potential canonical 6 is involved in macrophage inflammatory protein-2-induced migration of mouse neutrophils. *Acta Physiol.* **2009**, *195*, 3–11. [CrossRef] [PubMed]
80. Lindemann, O.; Umlauf, D.; Frank, S.; Schimmelpfennig, S.; Bertrand, J.; Pap, T.; Hanley, P.J.; Fabian, A.; Dietrich, A.; Schwab, A. TRPC6 regulates CXCR2-mediated chemotaxis of murine neutrophils. *J. Immunol.* **2013**, *190*, 5496–5505. [CrossRef] [PubMed]
81. Weber, E.W.; Han, F.; Tauseef, M.; Birnbaumer, L.; Mehta, D.; Muller, W.A. TRPC6 is the endothelial calcium channel that regulates leukocyte transendothelial migration during the inflammatory response. *J. Exp. Med.* **2015**. [CrossRef] [PubMed]
82. Singh, I.; Knezevic, N.; Ahmmed, G.U.; Kini, V.; Malik, A.B.; Mehta, D. Gαq-TRPC6-mediated Ca^{2+} entry induces RHOA activation and resultant endothelial cell shape change in response to thrombin. *J. Biol. Chem.* **2007**, *282*, 7833–7843. [CrossRef] [PubMed]
83. Kini, V.; Chavez, A.; Mehta, D. A new role for pten in regulating transient receptor potential canonical channel 6-mediated Ca^{2+} entry, endothelial permeability, and angiogenesis. *J. Biol. Chem.* **2010**, *285*, 33082–33091. [CrossRef] [PubMed]
84. Ramirez, G.; Sciorati, C.; Bozzolo, E.; Zagato, L.; Citterio, L.; Coletto, L.; Lanzani, C.; Rovere-Querini, P.; Sabbadini, M.; Manunta, P. TRPC6 and Neuropsychiatric SLE: From bedside to bench. In *Clinical and Experimental Rheumatology*; Clinical & Exper Rheumatology: Pisa, Italy, 2016; p. S67.
85. Ramirez, G.A.; Lanzani, C.; Bozzolo, E.P.; Citterio, L.; Zagato, L.; Casamassima, N.; Canti, V.; Sabbadini, M.G.; Rovere-Querini, P.; Manunta, P.; et al. TRPC6 gene variants and neuropsychiatric lupus. *J. Neuroimmunol.* **2015**, *288*, 21–24. [CrossRef] [PubMed]
86. Ulmann, L.; Hirbec, H.; Rassendren, F. P2X4 receptors mediate PGE2 release by tissue-resident macrophages and initiate inflammatory pain. *EMBO J.* **2010**, *29*, 2290–2300. [CrossRef] [PubMed]
87. Burnstock, G. P2X ion channel receptors and inflammation. *Purinergic Signal.* **2016**, *12*, 59–67. [CrossRef] [PubMed]
88. Savio, L.E.B.; de Andrade Mello, P.; da Silva, C.G.; Coutinho-Silva, R. The P2X7 receptor in inflammatory diseases: Angel or demon? *Front. Pharmacol.* **2018**, *9*, 52. [CrossRef] [PubMed]
89. Muller, T.; Vieira, R.P.; Grimm, M.; Durk, T.; Cicko, S.; Zeiser, R.; Jakob, T.; Martin, S.F.; Blumenthal, B.; Sorichter, S.; et al. A potential role for P2X7R in allergic airway inflammation in mice and humans. *Am. J. Respir. Cell Mol. Biol.* **2011**, *44*, 456–464. [CrossRef] [PubMed]
90. Labasi, J.M.; Petrushova, N.; Donovan, C.; McCurdy, S.; Lira, P.; Payette, M.M.; Brissette, W.; Wicks, J.R.; Audoly, L.; Gabel, C.A. Absence of the P2X7 receptor alters leukocyte function and attenuates an inflammatory response. *J. Immunol.* **2002**, *168*, 6436–6445. [CrossRef] [PubMed]
91. Hang, P.; Zhao, J.; Cai, B.; Tian, S.; Huang, W.; Guo, J.; Sun, C.; Li, Y.; Du, Z. Brain-derived neurotrophic factor regulates TRPC3/6 channels and protects against myocardial infarction in rodents. *Int. J. Biol. Sci.* **2015**, *11*, 536–545. [CrossRef] [PubMed]
92. Mizoguchi, Y.; Kato, T.A.; Seki, Y.; Ohgidani, M.; Sagata, N.; Horikawa, H.; Yamauchi, Y.; Sato-Kasai, M.; Hayakawa, K.; Inoue, R.; et al. Brain-derived neurotrophic factor (BDNF) induces sustained intracellular Ca^{2+} elevation through the up-regulation of surface transient receptor potential 3 (TRPC3) channels in rodent microglia. *J. Biol. Chem.* **2014**, *289*, 18549–18555. [CrossRef] [PubMed]
93. Wang, J.; Lu, Z.H.; Gabius, H.J.; Rohowsky-Kochan, C.; Ledeen, R.W.; Wu, G. Cross-linking of GM1 ganglioside by galectin-1 mediates regulatory T cell activity involving TRPC5 channel activation: Possible role in suppressing experimental autoimmune encephalomyelitis. *J. Immunol.* **2009**, *182*, 4036–4045. [CrossRef] [PubMed]

94. Alawi, K.M.; Russell, F.A.; Aubdool, A.A.; Srivastava, S.; Riffo-Vasquez, Y.; Baldissera, L., Jr.; Thakore, P.; Saleque, N.; Fernandes, E.S.; Walsh, D.A.; et al. Transient receptor potential canonical 5 (TRPC5) protects against pain and vascular inflammation in arthritis and joint inflammation. *Ann. Rheum. Dis.* **2017**, *76*, 252–260. [CrossRef] [PubMed]
95. Bertin, S.; Aoki-Nonaka, Y.; de Jong, P.R.; Nohara, L.L.; Xu, H.; Stanwood, S.R.; Srikanth, S.; Lee, J.; To, K.; Abramson, L.; et al. The ion channel TRPV1 regulates the activation and proinflammatory properties of Cd4(+) T cells. *Nat. Immunol.* **2014**, *15*, 1055–1063. [CrossRef] [PubMed]
96. Link, T.M.; Park, U.; Vonakis, B.M.; Raben, D.M.; Soloski, M.J.; Caterina, M.J. TRPV2 has a pivotal role in macrophage particle binding and phagocytosis. *Nat. Immunol.* **2010**, *11*, 232–239. [CrossRef] [PubMed]
97. Tomilin, V.N.; Cherezova, A.L.; Negulyaev, Y.A.; Semenova, S.B. TRPV5/V6 channels mediate Ca(2+) influx in jurkat T cells under the control of extracellular pH. *J. Cell. Biochem.* **2016**, *117*, 197–206. [CrossRef] [PubMed]
98. Kim, J.K.; Ko, J.H.; Nam, J.H.; Woo, J.E.; Min, K.M.; Earm, Y.E.; Kim, S.J. Higher expression of TRPM7 channels in murine mature B lymphocytes than immature cells. *Korean J. Physiol. Pharmacol.* **2005**, *9*, 69–75.
99. Jin, J.; Desai, B.N.; Navarro, B.; Donovan, A.; Andrews, N.C.; Clapham, D.E. Deletion of TRPM7 disrupts embryonic development and thymopoiesis without altering Mg^{2+} homeostasis. *Science* **2008**, *322*, 756–760. [CrossRef] [PubMed]
100. Wykes, R.C.; Lee, M.; Duffy, S.M.; Yang, W.; Seward, E.P.; Bradding, P. Functional transient receptor potential melastatin 7 channels are critical for human mast cell survival. *J. Immunol.* **2007**, *179*, 4045–4052. [CrossRef] [PubMed]
101. Huang, L.; Ng, N.M.; Chen, M.; Lin, X.; Tang, T.; Cheng, H.; Yang, C.; Jiang, S. Inhibition of TRPM7 channels reduces degranulation and release of cytokines in rat bone marrow-derived mast cells. *Int. J. Mol. Sci.* **2014**, *15*, 11817–11831. [CrossRef] [PubMed]
102. Schilling, T.; Miralles, F.; Eder, C. TRPM7 regulates proliferation and polarisation of macrophages. *J. Cell Sci.* **2014**, *127*, 4561–4566. [CrossRef] [PubMed]
103. Ryazanova, L.V.; Hu, Z.; Suzuki, S.; Chubanov, V.; Fleig, A.; Ryazanov, A.G. Elucidating the role of the TRPM7 alpha-kinase: TRPM7 kinase inactivation leads to magnesium deprivation resistance phenotype in mice. *Sci. Rep.* **2014**, *4*, 7599. [CrossRef] [PubMed]
104. Ravell, J.; Chaigne-Delalande, B.; Lenardo, M. X-linked immunodeficiency with magnesium defect, epstein-barr virus infection, and neoplasia disease: A combined immune deficiency with magnesium defect. *Curr. Opin. Pediatr.* **2014**, *26*, 713–719. [CrossRef] [PubMed]
105. Serafini, N.; Dahdah, A.; Barbet, G.; Demion, M.; Attout, T.; Gautier, G.; Arcos-Fajardo, M.; Souchet, H.; Jouvin, M.H.; Vrtovsnik, F.; et al. The TRPM4 channel controls monocyte and macrophage, but not neutrophil, function for survival in sepsis. *J. Immunol.* **2012**, *189*, 3689–3699. [CrossRef] [PubMed]
106. Vennekens, R.; Olausson, J.; Meissner, M.; Bloch, W.; Mathar, I.; Philipp, S.E.; Schmitz, F.; Weissgerber, P.; Nilius, B.; Flockerzi, V.; et al. Increased IGE-dependent mast cell activation and anaphylactic responses in mice lacking the calcium-activated nonselective cation channel TRPM4. *Nat. Immunol.* **2007**, *8*, 312–320. [CrossRef] [PubMed]
107. Weber, K.S.; Hildner, K.; Murphy, K.M.; Allen, P.M. TRPM4 differentially regulates th1 and TH2 function by altering calcium signaling and NFAT localization. *J. Immunol.* **2010**, *185*, 2836–2846. [CrossRef] [PubMed]
108. Barbet, G.; Demion, M.; Moura, I.C.; Serafini, N.; Leger, T.; Vrtovsnik, F.; Monteiro, R.C.; Guinamard, R.; Kinet, J.P.; Launay, P. The calcium-activated nonselective cation channel TRPM4 is essential for the migration but not the maturation of dendritic cells. *Nat. Immunol.* **2008**, *9*, 1148–1156. [CrossRef] [PubMed]
109. Moss, R.B.; Bocian, R.C.; Hsu, Y.P.; Dong, Y.J.; Kemna, M.; Wei, T.; Gardner, P. Reduced IL-10 secretion by Cd4+ T lymphocytes expressing mutant cystic fibrosis transmembrane conductance regulator (CFTR). *Clin. Exp. Immunol.* **1996**, *106*, 374–388. [CrossRef] [PubMed]
110. Zhu, J.; Yang, Y.; Hu, S.G.; Zhang, Q.B.; Yu, J.; Zhang, Y.M. T-lymphocyte KV1.3 channel activation triggers the NLRP3 inflammasome signaling pathway in hypertensive patients. *Exp. Ther. Med.* **2017**, *14*, 147–154. [CrossRef] [PubMed]
111. Stevens, A.; Yuasa, M.; Peckham, D.; Olsen, C.; Iadonato, S.; Probst, P. *Thu0285 Dalazatide, an Inhibitor of the KV1.3 Channel on Activated Effector Memory T Cells, Has Immunotherapy Potential in Systemic Lupus Erythematosus*; BMJ Publishing Group Ltd.: London, UK, 2016.

112. Tarcha, E.J.; Olsen, C.M.; Probst, P.; Peckham, D.; Munoz-Elias, E.J.; Kruger, J.G.; Iadonato, S.P. Safety and pharmacodynamics of dalazatide, a KV1.3 channel inhibitor, in the treatment of plaque psoriasis: A randomized phase 1b trial. *PLoS ONE* **2017**, *12*, e0180762. [CrossRef] [PubMed]
113. Grgic, I.; Wulff, H.; Eichler, I.; Flothmann, C.; Kohler, R.; Hoyer, J. Blockade of T-lymphocyte KCa3.1 and KV1.3 channels as novel immunosuppression strategy to prevent kidney allograft rejection. *Transplant. Proc.* **2009**, *41*, 2601–2606. [CrossRef] [PubMed]
114. Grgic, I.; Eichler, I.; Heinau, P.; Si, H.; Brakemeier, S.; Hoyer, J.; Kohler, R. Selective blockade of the intermediate-conductance Ca^{2+}-activated K^+ channel suppresses proliferation of microvascular and macrovascular endothelial cells and angiogenesis in vivo. *Arterioscler. Thromb. Vasc. Biol.* **2005**, *25*, 704–709. [CrossRef] [PubMed]
115. Chou, C.C.; Lunn, C.A.; Murgolo, N.J. KCa3.1: Target and marker for cancer, autoimmune disorder and vascular inflammation? *Expert Rev. Mol. Diagn.* **2008**, *8*, 179–187. [CrossRef] [PubMed]
116. Toyama, K.; Wulff, H.; Chandy, K.G.; Azam, P.; Raman, G.; Saito, T.; Fujiwara, Y.; Mattson, D.L.; Das, S.; Melvin, J.E.; et al. The intermediate-conductance calcium-activated potassium channel KCa3.1 contributes to atherogenesis in mice and humans. *J. Clin. Investig.* **2008**, *118*, 3025–3037. [CrossRef] [PubMed]
117. Buisman, H.P.; Steinberg, T.H.; Fischbarg, J.; Silverstein, S.C.; Vogelzang, S.A.; Ince, C.; Ypey, D.L.; Leijh, P.C. Extracellular ATP induces a large nonselective conductance in macrophage plasma membranes. *Proc. Natl. Acad. Sci. USA* **1988**, *85*, 7988–7992. [CrossRef] [PubMed]
118. Singh, C.R.; Moulton, R.A.; Armitige, L.Y.; Bidani, A.; Snuggs, M.; Dhandayuthapani, S.; Hunter, R.L.; Jagannath, C. Processing and presentation of a mycobacterial antigen 85b epitope by murine macrophages is dependent on the phagosomal acquisition of vacuolar proton ATPase and in situ activation of cathepsin D. *J. Immunol.* **2006**, *177*, 3250–3259. [CrossRef] [PubMed]
119. Rahgozar, K.; Wright, E.; Carrithers, L.M.; Carrithers, M.D. Mediation of protection and recovery from experimental autoimmune encephalomyelitis by macrophages expressing the human voltage-gated sodium channel nav1.5. *J. Neuropathol. Exp. Neurol.* **2013**, *72*, 489–504. [CrossRef] [PubMed]
120. Jiang, L.; Salao, K.; Li, H.; Rybicka, J.M.; Yates, R.M.; Luo, X.W.; Shi, X.X.; Kuffner, T.; Tsai, V.W.; Husaini, Y.; et al. Intracellular chloride channel protein clic1 regulates macrophage function through modulation of phagosomal acidification. *J. Cell Sci.* **2012**, *125*, 5479–5488. [CrossRef] [PubMed]
121. Medic, N.; Desai, A.; Olivera, A.; Abramowitz, J.; Birnbaumer, L.; Beaven, M.A.; Gilfillan, A.M.; Metcalfe, D.D. Knockout of the TRPC1 gene reveals that TRPC1 can promote recovery from anaphylaxis by negatively regulating mast cell TNF-alpha production. *Cell Calcium* **2013**, *53*, 315–326. [CrossRef] [PubMed]
122. Chung, S.A.; Brown, E.E.; Williams, A.H.; Ramos, P.S.; Berthier, C.C.; Bhangale, T.; Alarcon-Riquelme, M.E.; Behrens, T.W.; Criswell, L.A.; Graham, D.C.; et al. Lupus nephritis susceptibility loci in women with systemic lupus erythematosus. *J. Am. Soc. Nephrol.* **2014**. [CrossRef] [PubMed]
123. Nilius, B.; Owsianik, G. The transient receptor potential family of ion channels. *Genome Biol.* **2011**, *12*, 218. [CrossRef] [PubMed]
124. Freichel, M.; Almering, J.; Tsvilovskyy, V. The role of TRP proteins in mast cells. *Front. Immunol.* **2012**, *3*, 150. [CrossRef] [PubMed]
125. Montell, C.; Rubin, G.M. Molecular characterization of the drosophila TRP locus: A putative integral membrane protein required for phototransduction. *Neuron* **1989**, *2*, 1313–1323. [CrossRef]
126. Dietrich, A.; Chubanov, V.; Kalwa, H.; Rost, B.R.; Gudermann, T. Cation channels of the transient receptor potential superfamily: Their role in physiological and pathophysiological processes of smooth muscle cells. *Pharmacol. Ther.* **2006**, *112*, 744–760. [CrossRef] [PubMed]
127. Dietrich, A.; Fahlbusch, M.; Gudermann, T. Classical transient receptor potential 1 (TRPC1): Channel or channel regulator? *Cells* **2014**, *3*, 939–962. [CrossRef] [PubMed]
128. Kim, M.S.; Zeng, W.; Yuan, J.P.; Shin, D.M.; Worley, P.F.; Muallem, S. Native store-operated Ca^{2+} influx requires the channel function of orai1 and TRPC1. *J. Biol. Chem.* **2009**, *284*, 9733–9741. [CrossRef] [PubMed]
129. Ambudkar, I.S.; Ong, H.L.; Liu, X.; Bandyopadhyay, B.; Cheng, K.T. TRPC1: The link between functionally distinct store-operated calcium channels. *Cell Calcium* **2007**, *42*, 213–223. [CrossRef] [PubMed]
130. Storch, U.; Forst, A.L.; Philipp, M.; Gudermann, T.; Mederos y Schnitzler, M. Transient receptor potential channel 1 (TRPC1) reduces calcium permeability in heteromeric channel complexes. *J. Biol. Chem.* **2012**, *287*, 3530–3540. [CrossRef] [PubMed]

131. Vassilieva, I.O.; Tomilin, V.N.; Marakhova, I.I.; Shatrova, A.N.; Negulyaev, Y.A.; Semenova, S.B. Expression of transient receptor potential vanilloid channels TRPV5 and TRPV6 in human blood lymphocytes and Jurkat leukemia T cells. *J. Membr. Biol.* **2013**, *246*, 131–140. [CrossRef] [PubMed]
132. Ma, H.T.; Peng, Z.; Hiragun, T.; Iwaki, S.; Gilfillan, A.M.; Beaven, M.A. Canonical transient receptor potential 5 channel in conjunction with orai1 and stim1 allows Sr^{2+} entry, optimal influx of Ca^{2+}, and degranulation in a rat mast cell line. *J. Immunol.* **2008**, *180*, 2233–2239. [CrossRef] [PubMed]
133. Van Abel, M.; Hoenderop, J.G.; Bindels, R.J. The epithelial calcium channels TRPV5 and TRPV6: Regulation and implications for disease. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **2005**, *371*, 295–306. [CrossRef] [PubMed]
134. Soboloff, J.; Spassova, M.; Xu, W.; He, L.P.; Cuesta, N.; Gill, D.L. Role of endogenous TRPC6 channels in Ca^{2+} signal generation in A7R5 smooth muscle cells. *J. Biol. Chem.* **2005**, *280*, 39786–39794. [CrossRef] [PubMed]
135. Guilbert, A.; Dhennin-Duthille, I.; Hiani, Y.E.; Haren, N.; Khorsi, H.; Sevestre, H.; Ahidouch, A.; Ouadid-Ahidouch, H. Expression of TRPC6 channels in human epithelial breast cancer cells. *BMC Cancer* **2008**, *8*, 125. [CrossRef] [PubMed]
136. Yang, L.L.; Liu, B.C.; Lu, X.Y.; Yan, Y.; Zhai, Y.J.; Bao, Q.; Doetsch, P.W.; Deng, X.; Thai, T.L.; Alli, A.A.; et al. Inhibition of TRPC6 reduces non-small cell lung cancer cell proliferation and invasion. *Oncotarget* **2017**, *8*, 5123–5134. [CrossRef] [PubMed]
137. Wen, L.; Liang, C.; Chen, E.; Chen, W.; Liang, F.; Zhi, X.; Wei, T.; Xue, F.; Li, G.; Yang, Q.; et al. Regulation of multi-drug resistance in hepatocellular carcinoma cells is TRPC6/calcium dependent. *Sci. Rep.* **2016**, *6*, 23269. [CrossRef] [PubMed]
138. Wang, D.; Li, X.; Liu, J.; Li, J.; Li, L.J.; Qiu, M.X. Effects of TRPC6 on invasibility of low-differentiated prostate cancer cells. *Asian Pac. J. Trop. Med.* **2014**, *7*, 44–47. [CrossRef]
139. Zhang, S.S.; Wen, J.; Yang, F.; Cai, X.L.; Yang, H.; Luo, K.J.; Liu, Q.W.; Hu, R.G.; Xie, X.; Huang, Q.Y.; et al. High expression of transient potential receptor C6 correlated with poor prognosis in patients with esophageal squamous cell carcinoma. *Med. Oncol.* **2013**, *30*, 607. [CrossRef] [PubMed]
140. Song, J.; Wang, Y.; Li, X.; Shen, Y.; Yin, M.; Guo, Y.; Diao, L.; Liu, Y.; Yue, D. Critical role of TRPC6 channels in the development of human renal cell carcinoma. *Mol. Biol. Rep.* **2013**, *40*, 5115–5122. [CrossRef] [PubMed]
141. Amin, M.R.; Piplani, H.; Sharma, T.; Mehta, D. Switching off TRPC6 signaling: A new anti-edemagenic strategy. *FASEB J.* **2017**, *31*, 676.4.
142. Chen, W.; Oberwinkler, H.; Werner, F.; Gassner, B.; Nakagawa, H.; Feil, R.; Hofmann, F.; Schlossmann, J.; Dietrich, A.; Gudermann, T.; et al. Atrial natriuretic peptide-mediated inhibition of microcirculatory endothelial Ca^{2+} and permeability response to histamine involves CGMP-dependent protein kinase I and TRPC6 channels. *Arterioscler. Thromb. Vasc. Biol.* **2013**, *33*, 2121–2129. [CrossRef] [PubMed]
143. Tauseef, M.; Knezevic, N.; Chava, K.R.; Smith, M.; Sukriti, S.; Gianaris, N.; Obukhov, A.G.; Vogel, S.M.; Schraufnagel, D.E.; Dietrich, A.; et al. TLR4 activation of TRPC6-dependent calcium signaling mediates endotoxin-induced lung vascular permeability and inflammation. *J. Exp. Med.* **2012**, *209*, 1953–1968. [CrossRef] [PubMed]
144. Finney-Hayward, T.K.; Popa, M.O.; Bahra, P.; Li, S.; Poll, C.T.; Gosling, M.; Nicholson, A.G.; Russell, R.E.; Kon, O.M.; Jarai, G.; et al. Expression of transient receptor potential c6 channels in human lung macrophages. *Am. J. Respir. Cell Mol. Biol.* **2010**, *43*, 296–304. [CrossRef] [PubMed]
145. Carrillo, C.; Hichami, A.; Andreoletti, P.; Cherkaoui-Malki, M.; del Mar Cavia, M.; Abdoul-Azize, S.; Alonso-Torre, S.R.; Khan, N.A. Diacylglycerol-containing oleic acid induces increases in [Ca(2+)](i) via TRPC3/6 channels in human T-cells. *Biochim. Biophys. Acta* **2012**, *1821*, 618–626. [CrossRef] [PubMed]
146. Wu, Q.-Y.; Sun, M.-R.; Wu, C.-L.; Li, Y.; Du, J.-J.; Zeng, J.-Y.; Bi, H.-L.; Sun, Y.-H. Activation of calcium-sensing receptor increases TRPC3/6 expression in T lymphocyte in sepsis. *Mol. Immunol.* **2015**, *64*, 18–25. [CrossRef] [PubMed]
147. Sel, S.; Rost, B.R.; Yildirim, A.O.; Sel, B.; Kalwa, H.; Fehrenbach, H.; Renz, H.; Gudermann, T.; Dietrich, A. Loss of classical transient receptor potential 6 channel reduces allergic airway response. *Clin. Exp. Allergy* **2008**, *38*, 1548–1558. [CrossRef] [PubMed]
148. Zhang, Y.; Qin, W.; Zhang, L.; Wu, X.; Du, N.; Hu, Y.; Li, X.; Shen, N.; Xiao, D.; Zhang, H.; et al. Microrna-26a prevents endothelial cell apoptosis by directly targeting TRPC6 in the setting of atherosclerosis. *Sci. Rep.* **2015**, *5*, 9401. [CrossRef] [PubMed]

149. Bouts, Y.M.; Wolthuis, D.F.; Dirkx, M.F.; Pieterse, E.; Simons, E.M.; van Boekel, A.M.; Dieker, J.W.; van der Vlag, J. Apoptosis and net formation in the pathogenesis of SLE. *Autoimmunity* **2012**, *45*, 597–601. [CrossRef] [PubMed]
150. Dieker, J.; Tel, J.; Pieterse, E.; Thielen, A.; Rother, N.; Bakker, M.; Fransen, J.; Dijkman, H.B.; Berden, J.H.; de Vries, J.M.; et al. Circulating apoptotic microparticles in systemic lupus erythematosus patients drive the activation of dendritic cell subsets and prime neutrophils for netosis. *Arthritis Rheumatol.* **2016**, *68*, 462–472. [CrossRef] [PubMed]
151. Souliotis, V.L.; Sfikakis, P.P. Increased DNA double-strand breaks and enhanced apoptosis in patients with lupus nephritis. *Lupus* **2015**, *24*, 804–815. [CrossRef] [PubMed]
152. Lu, M.C.; Lai, N.S.; Yu, H.C.; Hsieh, S.C.; Tung, C.H.; Yu, C.L. Nifedipine suppresses TH1/TH2 cytokine production and increased apoptosis of anti-Cd3 + anti-Cd28-activated mononuclear cells from patients with systemic lupus erythematosus via calcineurin pathway. *Clin. Immunol.* **2008**, *129*, 462–470. [CrossRef] [PubMed]
153. Ramanathan, G.; Mannhalter, C. Increased expression of transient receptor potential canonical 6 (TRPC6) in differentiating human megakaryocytes. *Cell Biol. Int.* **2016**, *40*, 223–231. [CrossRef] [PubMed]
154. Vemana, H.P.; Karim, Z.A.; Conlon, C.; Khasawneh, F.T. A critical role for the transient receptor potential channel type 6 in human platelet activation. *PLoS ONE* **2015**, *10*, e0125764. [CrossRef] [PubMed]
155. Espinosa, E.V.P.; Murad, J.P.; Ting, H.J.; Khasawneh, F.T. Mouse transient receptor potential channel 6: Role in hemostasis and thrombogenesis. *Biochem. Biophys. Res. Commun.* **2012**, *417*, 853–856. [CrossRef] [PubMed]
156. Semple, J.W.; Italiano, J.E., Jr.; Freedman, J. Platelets and the immune continuum. *Nat. Rev. Immunol.* **2011**, *11*, 264–274. [CrossRef] [PubMed]
157. Nurden, A.T. Platelets, inflammation and tissue regeneration. *Thromb. Haemost.* **2011**, *105*, S13–S33. [CrossRef] [PubMed]
158. Maugeri, N.; Baldini, M.; Rovere-Querini, P.; Maseri, A.; Sabbadini, M.G.; Manfredi, A.A. Leukocyte and platelet activation in patients with giant cell arteritis and polymyalgia rheumatica: A clue to thromboembolic risks? *Autoimmunity* **2009**, *42*, 386–388. [CrossRef] [PubMed]
159. Ramirez, G.A.; Rovere-Querini, P.; Sabbadini, M.G.; Manfredi, A.A. Parietal and intravascular innate mechanisms of vascular inflammation. *Arthritis Res. Ther.* **2015**, *17*, 16. [CrossRef] [PubMed]
160. Mantovani, A.; Cassatella, M.A.; Costantini, C.; Jaillon, S. Neutrophils in the activation and regulation of innate and adaptive immunity. *Nat. Rev. Immunol.* **2011**, *11*, 519–531. [CrossRef] [PubMed]
161. Scherlinger, M.; Guillotin, V.; Truchetet, M.E.; Contin-Bordes, C.; Sisirak, V.; Duffau, P.; Lazaro, E.; Richez, C.; Blanco, P. Systemic lupus erythematosus and systemic sclerosis: All roads lead to platelets. *Autoimmun. Rev.* **2018**, *17*, 625–635. [CrossRef] [PubMed]
162. Weissmann, N.; Sydykov, A.; Kalwa, H.; Storch, U.; Fuchs, B.; Mederos y Schnitzler, M.; Brandes, R.P.; Grimminger, F.; Meissner, M.; Freichel, M.; et al. Activation of TRPC6 channels is essential for lung ischaemia-reperfusion induced oedema in mice. *Nat. Commun.* **2012**, *3*, 649. [CrossRef] [PubMed]
163. Malczyk, M.; Erb, A.; Veith, C.; Ghofrani, H.A.; Schermuly, R.T.; Gudermann, T.; Dietrich, A.; Weissmann, N.; Sydykov, A. The role of transient receptor potential channel 6 channels in the pulmonary vasculature. *Front. Immunol.* **2017**, *8*, 707. [CrossRef] [PubMed]
164. Urban, N.; Hill, K.; Wang, L.; Kuebler, W.M.; Schaefer, M. Novel pharmacological TRPC inhibitors block hypoxia-induced vasoconstriction. *Cell Calcium* **2012**, *51*, 194–206. [CrossRef] [PubMed]
165. Lu, W.; Wang, J.; Shimoda, L.A.; Sylvester, J.T. Differences in STIM1 and TRPC expression in proximal and distal pulmonary arterial smooth muscle are associated with differences in Ca^{2+} responses to hypoxia. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2008**, *295*, L104–L113. [CrossRef] [PubMed]
166. Wang, J.; Shimoda, L.A.; Weigand, L.; Wang, W.; Sun, D.; Sylvester, J.T. Acute hypoxia increases intracellular $[Ca^{2+}]$ in pulmonary arterial smooth muscle by enhancing capacitative Ca^{2+} entry. *Am. J. Physiol. Lung Cell. Mol. Physiol.* **2005**, *288*, L1059–L1069. [CrossRef] [PubMed]
167. Jung, S.; Strotmann, R.; Schultz, G.; Plant, T.D. TRPC6 is a candidate channel involved in receptor-stimulated cation currents in A7R5 smooth muscle cells. *Am. J. Physiol. Cell Physiol.* **2002**, *282*, C347–C359. [CrossRef] [PubMed]
168. Erac, Y.; Selli, C.; Kosova, B.; Akcali, K.C.; Tosun, M. Expression levels of TRPC1 and TRPC6 ion channels are reciprocally altered in aging rat aorta: Implications for age-related vasospastic disorders. *Age* **2010**, *32*, 223–230. [CrossRef] [PubMed]

169. Li, W.; Chen, X.; Riley, A.M.; Hiett, S.C.; Temm, C.J.; Beli, E.; Long, X.; Chakraborty, S.; Alloosh, M.; White, F.A.; et al. Long-term spironolactone treatment reduces coronary TRPC expression, vasoconstriction, and atherosclerosis in metabolic syndrome pigs. *Basic Res. Cardiol.* **2017**, *112*, 54. [CrossRef] [PubMed]
170. He, X.; Li, S.; Liu, B.; Susperreguy, S.; Formoso, K.; Yao, J.; Kang, J.; Shi, A.; Birnbaumer, L.; Liao, Y. Major contribution of the 3/6/7 class of TRPC channels to myocardial ischemia/reperfusion and cellular hypoxia/reoxygenation injuries. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, E4582–E4591. [CrossRef] [PubMed]
171. Zhou, R.; Hang, P.; Zhu, W.; Su, Z.; Liang, H.; Du, Z. Whole genome network analysis of ion channels and connexins in myocardial infarction. *Cell. Physiol. Biochem. Int. J. Exp. Cell. Physiol. Biochem. Pharmacol.* **2011**, *27*, 299–304. [CrossRef] [PubMed]
172. Kuwahara, K.; Wang, Y.; McAnally, J.; Richardson, J.A.; Bassel-Duby, R.; Hill, J.A.; Olson, E.N. TRPC6 fulfills a calcineurin signaling circuit during pathologic cardiac remodeling. *J. Clin. Investig.* **2006**, *116*, 3114–3126. [CrossRef] [PubMed]
173. Eder, P. Cardiac remodeling and disease: SOCE and TRPC signaling in cardiac pathology. *Adv. Exp. Med. Biol.* **2017**, *993*, 505–521. [PubMed]
174. Shen, B.; He, Y.; Zhou, S.; Zhao, H.; Mei, M.; Wu, X. TRPC6 may protect renal ischemia-reperfusion injury through inhibiting necroptosis of renal tubular epithelial cells. *Med. Sci. Monit. Int. Med. J. Exp. Clin. Res.* **2016**, *22*, 633. [CrossRef]
175. Li, W.; Ding, Y.; Smedley, C.; Wang, Y.; Chaudhari, S.; Birnbaumer, L.; Ma, R. Increased glomerular filtration rate and impaired contractile function of mesangial cells in TRPC6 knockout mice. *Sci. Rep.* **2017**, *7*, 4145. [CrossRef] [PubMed]
176. Graham, S.; Gorin, Y.; Abboud, H.E.; Ding, M.; Lee, D.Y.; Shi, H.; Ding, Y.; Ma, R. Abundance of TRPC6 protein in glomerular mesangial cells is decreased by ROS and PKC in diabetes. *Am. J. Physiol. Cell Physiol.* **2011**, *301*, C304–C315. [CrossRef] [PubMed]
177. Santin, S.; Ars, E.; Rossetti, S.; Salido, E.; Silva, I.; Garcia-Maset, R.; Gimenez, I.; Ruiz, P.; Mendizabal, S.; Luciano Nieto, J.; et al. TRPC6 mutational analysis in a large cohort of patients with focal segmental glomerulosclerosis. *Nephrol. Dial. Transplant. Off. Publ. Eur. Dial. Transpl. Assoc. Eur. Ren. Assoc.* **2009**, *24*, 3089–3096. [CrossRef] [PubMed]
178. Winn, M.P.; Conlon, P.J.; Lynn, K.L.; Farrington, M.K.; Creazzo, T.; Hawkins, A.F.; Daskalakis, N.; Kwan, S.Y.; Ebersviller, S.; Burchette, J.L.; et al. A mutation in the TRPC6 cation channel causes familial focal segmental glomerulosclerosis. *Science* **2005**, *308*, 1801–1804. [CrossRef] [PubMed]
179. Kim, E.Y.; Yazdizadeh Shotorbani, P.; Dryer, S.E. TRPC6 inactivation confers protection in a model of severe nephrosis in rats. *J. Mol. Med.* **2018**, *96*, 631–644. [CrossRef] [PubMed]
180. Krall, P.; Canales, C.P.; Kairath, P.; Carmona-Mora, P.; Molina, J.; Carpio, J.D.; Ruiz, P.; Mezzano, S.A.; Li, J.; Wei, C.; et al. Podocyte-specific overexpression of wild type or mutant TRPC6 in mice is sufficient to cause glomerular disease. *PLoS ONE* **2010**, *5*, e12859. [CrossRef] [PubMed]
181. Dos Santos, M.; Bringhenti, R.N.; Rodrigues, P.G.; do Nascimento, J.F.; Pereira, S.V.; Zancan, R.; Monticielo, O.A.; Gasparin, A.A.; de Castro, W.P.; Veronese, F.V. Podocyte-associated mRNA profiles in kidney tissue and in urine of patients with active lupus nephritis. *Int. J. Clin. Exp. Pathol.* **2015**, *8*, 4600–4613. [PubMed]
182. Wu, Y.L.; Xie, J.; An, S.W.; Oliver, N.; Barrezueta, N.X.; Lin, M.H.; Birnbaumer, L.; Huang, C.L. Inhibition of TRPC6 channels ameliorates renal fibrosis and contributes to renal protection by soluble klotho. *Kidney Int.* **2017**, *91*, 830–841. [CrossRef] [PubMed]
183. Davis, J.; Burr, A.R.; Davis, G.F.; Birnbaumer, L.; Molkentin, J.D. A TRPC6-dependent pathway for myofibroblast transdifferentiation and wound healing in vivo. *Dev. Cell* **2012**, *23*, 705–715. [CrossRef] [PubMed]
184. Hofmann, K.; Fiedler, S.; Vierkotten, S.; Weber, J.; Klee, S.; Jia, J.; Zwickenpflug, W.; Flockerzi, V.; Storch, U.; Yildirim, A.O.; et al. Classical transient receptor potential 6 (TRPC6) channels support myofibroblast differentiation and development of experimental pulmonary fibrosis. *Biochim. Biophys. Acta* **2017**, *1863*, 560–568. [CrossRef] [PubMed]
185. Kurahara, L.H.; Sumiyoshi, M.; Aoyagi, K.; Hiraishi, K.; Nakajima, K.; Nakagawa, M.; Hu, Y.; Inoue, R. Intestinal myofibroblast TRPC6 channel may contribute to stenotic fibrosis in crohn's disease. *Inflamm. Bowel Dis.* **2015**, *21*, 496–506. [CrossRef] [PubMed]

186. Du, W.; Huang, J.; Yao, H.; Zhou, K.; Duan, B.; Wang, Y. Inhibition of TRPC6 degradation suppresses ischemic brain damage in rats. *J. Clin. Investig.* **2010**, *120*, 3480–3492. [CrossRef] [PubMed]
187. Li, H.; Huang, J.; Du, W.; Jia, C.; Yao, H.; Wang, Y. TRPC6 inhibited NMDA receptor activities and protected neurons from ischemic excitotoxicity. *J. Neurochem.* **2012**, *123*, 1010–1018. [CrossRef] [PubMed]
188. Zhang, J.; Mao, X.; Zhou, T.; Cheng, X.; Lin, Y. IL-17a contributes to brain ischemia reperfusion injury through calpain-TRPC6 pathway in mice. *Neuroscience* **2014**, *274*, 419–428. [CrossRef] [PubMed]
189. Griesi-Oliveira, K.; Acab, A.; Gupta, A.R.; Sunaga, D.Y.; Chailangkarn, T.; Nicol, X.; Nunez, Y.; Walker, M.F.; Murdoch, J.D.; Sanders, S.J.; et al. Modeling non-syndromic autism and the impact of TRPC6 disruption in human neurons. *Mol. Psychiatry* **2015**, *20*, 1350–1365. [CrossRef] [PubMed]
190. Zhang, H.; Sun, S.; Wu, L.; Pchitskaya, E.; Zakharova, O.; Fon Tacer, K.; Bezprozvanny, I. Store-operated calcium channel complex in postsynaptic spines: A new therapeutic target for Alzheimer's disease treatment. *J. Neurosci. Off. J. Soc. Neurosci.* **2016**, *36*, 11837–11850. [CrossRef] [PubMed]