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Emerging Signaling Concepts in Human (PATHO)Physiology

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Preface

Because recapitulation of the historic developments within a scientific field usually helps, or may even be required, for understanding current paradigms and concepts, it appears important to begin with a condensed historic overview characterizing a research area, which has gained an impressive amount of attention due to its impact on various aspects of cell biology.

During the past decades, the concept of *store-operated Ca^{2+} entry* as a pivotal component of cellular signaling in a wide range of biological systems and as a process of particular importance for human pathology has emerged slowly and with several critical milestones being accomplished only after a tedious process of knowledge acquisition. All of this started with the perception of a Ca^{2+} transport process that appeared initially to be important only for the more or less direct refilling of intracellular storage compartments. Mobilization or, in other words, discharge of Ca^{2+} from these storage sites had already been recognized as a crucial signaling step for the control of cellular functions, and the mechanism of recharging of these signaling elements had been envisaged as a process similar to the charging of an electrical capacitator by the capacitative current. Thus, the initial term created to describe the phenomenon was "*capacitative Ca^{2+} entry*", originally coined by Jim Putney Jr. in 1986. The understanding that the Ca^{2+} store refilling mechanism is actually associated with highly relevant increases in cytosolic Ca^{2+} and the discovery of the striking dependency of the trans-plasmalemmal Ca^{2+} flux on the filling state of the endoplasmic reticulum, representing the primarily involved Ca^{2+} storage organelle, led to the concept of "store-operated Ca^{2+} entry" (SOCE) as a (patho)physiologically important signaling pathway.

Elucidation of the molecular basis of this cellular mechanism was promoted by the identification of the ion conductance mediating SOCE in mast cells. This conductance, which was originally designated as calcium release-activated calcium conductance (CRAC) by Markus Hoth and Reinhold Penner in 1992, was characterized as highly Ca^{2+} selective and mediated by an ion channel of particularly low unitary conductance, which suggested attempts to analyze the properties at the molecular, single channel level as barely feasible. Subsequent investigations in a wide range of tissues and cell types revealed ubiquitous expression of the signaling phenomenon, along with inconsistencies regarding the biophysical properties of the involved channels. Uncertainty about the pore features of store-operated membrane conductances, along with an even more disturbing uncertainty

regarding the mechanism(s) by which information on the filling state of the Ca^{2+} store is transferred to the Ca^{2+} entry channel has puzzled scientists in the field until the recent discovery of a paradigm SOCE channel.

A signal complex comprised of a highly Ca^{2+} selective pore protein (Orai1) and a Ca^{2+} sensor protein (STIM1) bridges the gap between plasma membrane and endoplasmic reticulum, and enables the information flow required for store-operated gating of the channels in immune cells and probably in many other tissues. This recently gained knowledge on the mechanistic principles underlying a classical SOCE pathway is currently promoting further expansion of the field and inspires investigators to fully elucidate the molecular mechanism of SOCE in different cell types, including rigorous analyses of the role of additional signaling molecules involved in these phenomena and elucidation of the crosstalk of SOCE with other Ca^{2+} signaling mechanisms. Moreover, recent progress in SOCE research, specifically the emerging general agreement on certain molecular concepts, has encouraged attempts to develop therapeutic strategies based on SOCE as a target. This research includes the extensive evaluation of the role of SOCE pathways in human pathology. At this point, having passed important milestones and in expectation of further expansion of SOCE research into a variety of biomedical fields, this book was intended to provide an overview on three main aspects SOCE research.

SOCE signaling is based on exceptional intracellular communication machinery, the key parts of which have just recently been uncovered, is introduced in Part I of this book. Part II provides information on how SOCE is currently seen as a component of cellular Ca^{2+} signaling networks and a pivotal determinant of organelle Ca^{2+} handling. Finally, current evidence for the (patho)physiological significance of SOCE in a selection of organ systems and tissues is outlined in Part III. Because molecular mechanisms, their integration within the cell's signaling network and (patho)physiological aspects of SOCE are highly integrated issues, the reader will recognize a certain degree of intended and potentially useful overlap, which is highlighted within the chapters by cross-references. Thereby, the book is expected to provide a valuable synopsis including the most relevant scientific points of view, specifically those of molecular biophysics, cell biology and pathology.

Finally, the editors would like to express their sincere thanks and appreciation to all contributors for their dedicated collaboration in this project and also to Karin Osibow for her support in editing this book.

We hope that the information provided by this book will be helpful for both students and advanced scientists that are new in the field as well as inspiring for researchers in a wide range of related areas.

Graz/Linz, November 2011 K. Groschner, W.F. Graier and C. Romanin

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Abbreviations

$\Delta\Psi_m$	Mitochondrial membrane potential
$[Ca^{2+}]_{cyt;\ c}$	Cytosolic Ca^{2+} concentration
$[Ca^{2+}]_{ER}$	Free Ca^{2+} concentration of the ER
$[Ca^{2+}]_i$	Intracellular free Ca^{2+} concentration
$[Ca^{2+}]_m$	Mitochondrial Ca^{2+} concentration
2-APB	2-aminoethoxydiphenyl borate
AA	Arachidonic acid
AC	Adenylyl cyclase
ACTH	Adrenocorticotropic hormone
AD	Alzheimer's disease
AIHA	Autoimmune haemolytic anemia
ALS	Amyotrophic lateral sclerosis
ANF/ANP	Atrial natriuretic factor/peptide
Ang-II	Angiotensin II
APP	Amyloid precursor protein
ARC	Arachidonate-regulated channel
BAPTA	(1,2-bis(o-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid)
BCR	B cell receptor
BHQ	2,5-di-(tert-butyl)-1,4-benzohydroquinone
BKCa	Big conductance Ca^{2+}-activated K^+ channels
BNP	Brain natriuretic peptide
Btk	Bruton's tyrosine kinase
BP	Blood pressure
CAD	CRAC-activating domain
CaM	Calmodulin
CamK	Ca^{2+}/CaM dependent protein kinase
CaN	Calcineurin
cat-SOC	Cation store-operated channel
Cav1.2	L-type voltage-operated Ca^{2+} channel 1.2
CC	Coiled-coil
CCD	Central core disease
CCE	Capacitative Ca^{2+} entry
CDI	Ca^{2+}-dependent inactivation
CECR	Ca^{2+} entry Ca^{2+} refilling
CIF	Ca^{2+} influx factor

CIRB	CaM and IP_3R binding site
CMD	CRAC modulatory domain
CMV	Cytomegalovirus
CNS	Central nervous system
CPA	Cyclopiazonic acid
CPAE	Calf pulmonary endothelial cells
CRAC	Ca^{2+} release-activated Ca^{2+} channel
CRACR2A	CRAC regulator2A
CREB	cAMP response element-binding transcription factor
CsA	Cyclosporine A
CO	Cytochrome oxidase
DAG	Diacylglycerol
DM2	Type 2 Diabetes mellitus
DMD	Duchenne muscular dystrophy
DPI	Diphenyliodonium
DTS	Dense tubular system
EAE	Experimental autoimmune encephalomyelitis
EBV	Epstein-Barr virus
EC	Endothelial cell
ECCE	Excitation coupled Ca^{2+} entry
EDA	Ectodermal dysplasia with anhydrosis
EDCF	Endothelium-derived contracting factor
EDRF	Endothelium-derived relaxing factor
5,6-EET	5,6-epoxyeicosatrienoic acid
EFh	EF hand
EGTA	Ethylene Glycol-bis(ß-Aminoethylether)-N,N,N′,N′-Tetraacetic acid
eNOS	Endothelial NO synthase (NOS III)
ER	Endoplasmic reticulum
ERM	Ezrin-radixin-moesin
ET-1	Endothelin 1
ETC	Excitation-transcription coupling
FAD	Familial Alzheimer's disease
FCCP	Carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone
FRET	Förster/fluorescence resonance energy transfer
GECI	Genetically-encoded Ca^{2+}-sensitive indicators
GPCR	G-protein coupled receptor
GRC	Growth factor regulated channel
HCMD	High-Ca^{2+} microdomain
HD	Huntington's disease
20-HETE	20-Hydroxyeicosatetraenoic acid
HIV	Human immunodeficiency virus
HMEC	Human microvascular endothelial cell
HPAEC	Human pulmonary artery EC
HSCT	Hematopoietic stem cell transplantation
HUVEC	Human umbilical vein EC

I_{CaL}	L-type Ca^{2+} current
I_{CRAC}	Ca^{2+} release activated Ca^{2+} currents
I_{SOC}	Store-operated Ca^{2+} current
IML	Intermembrane loop
IMM	Inner mitochondrial membrane
IP_3; $InsP_3$	Inositol 1,4,5-trisphosphate
IP_3R; $InsP_3R$	IP_3 receptor
Itk	IL2-inducible T cell kinase
KCa	Ca^{2+}-activated K^+ channels
KS	Kaposi sarcoma
LAT	Linker for activation of T cells
LBs	Lewy bodies
LGC	Ligand-gated cation channels
LGMD	Limb-Girdle muscular dystrophy
LNats	Local sub-PM $[Na^+]_i$ transients
LTCC	L-type Ca^{2+} channels
LysoPLs/LPL	Lysophospholipids
MBP	Myelin basic protein
MCU	Mitochondrial Ca^{2+} uniporter
MICU1	Mitochondrial calcium uptake 1
MLCK	Myosin light chain kinase
MS	Multiple sclerosis
MSC	Mechanosensitive channel
mitoNOS	Mitochondria-specific NO synthase
mNCX	Mitochondrial Na^+/Ca^{2+} exchanger
mNHE	Mitochondrial Na^+/H^+ exchanger
mPTP	Mitochondrial permeability transition pore
mTOR	Mammalian target of rapamycin
NAADP	Nicotinic acid adenine dinucleaotide phosphate
NCX	Na^+/Ca^{2+} exchanger
NCKX	Na^+/Ca^{2+}-K^+ exchanger
NFAT	Nuclear factor of activated T cells
NFkB	Nuclear factor kappa-light-chain-enhancer of activated B-cells
NOX	NADPH oxidase
NRSF	Neuron-restrictive silencer factor
NSC	Neuronal stem cell
NSCC	Non-selective cation channels
OASF	Orai-activating small fragment
OMM	Outer mitochondrial membrane
PAH	Pulmonary arterial hypertension
PASMC	Pulmonary artery smooth muscle cell
PD	Parkinson's disease
PDGF	Platelet-derived growth factor
PIP_2	Phosphatidylinositol 4,5 bisphosphate
PKA	Protein kinase A

PKC	Protein kinase C
PLA_2	Phospholipase A_2
PLC	Phospholipase C
PM	Plasma membrane
PMA	Phorbol myristate acetate
PMCA	Plasma membrane Ca^{2+} ATPase
PS	Preseniline
PtdCh	Phosphatidyl choline
RACK1	Receptor for activated C-kinase-1
RBL	Rat basophil leukaemia (cell)
ROC	Receptor-operated Ca^{2+}channels
ROCE	Receptor-operated Ca^{2+} entry
ROS	Reactive oxygen species
RR	Ruthenium red
RTK	Receptor tyrosine kinase
RyR	Ryanodine receptor
SAC	Stretch-activated cation channels
SACE	Stretch-activated Ca^{2+} entry
SAM	Sterile alpha motif
SCA	Spinocerebellar ataxias
SCID	Severe combined immune deficiency
SD	Sporadic Alzheimer's disease
SERCA	Sarcoplasmic/endoplasmic-reticulum Ca^{2+}-ATPase
SHR	Spontaneously hypertensive rats
Sig	Signal peptide
SMC	Smooth muscle cell
SNAP25	Synaptosome-associated protein 25
SNP	Sodium nitroprusside
S/P	Serine-/prolin-rich
Sp1P	Sphingosine-1-phosphate
SPCA	Secretory pathway Ca^{2+} ATPase
SPL	Subplasmalemmal
SOAR	STIM1 Orai-activating region
SOC	Store-operated channel
SOCC	Store-operated Ca^{2+} channel
SOCE	Store-operated entry
SOCIC	Store-operated Ca^{2+} influx complex
SOD	Superoxide dismutase
SR	Sarcoplasmic reticulum
STIM1	Stromal interaction molecule 1
TBHQ	2,5-di-(tert-butyl)-1,4-benzohydroquinone
TCR	T cell receptor
Tg	Thapsigargin
TIRF	Total internal reflection fluorescence
TPC	Two-pore domain channel

TPR	Total peripheral vascular resistance
TRP	Transient receptor potential
TRPC	Transient receptor potential canonical family of ion channels
TIRF	Total internal reflection fluorescence
TM	Transmembrane
Treg	Regulatory T cells
UPC	Uncoupling protein
VDAC	Voltage-dependent anion channel
VEC	Vascular endothelial cell
VEGF	Vascular endothelial growth factor
VEGFR	VEGF receptor
VGCC	Voltage gated Ca^{2+} channels
ZAP-70	Z-chain associated protein kinase 70

Part I

SOCE: Fundamental Mechanistic Concepts

Introduction

1

James W. Putney

This volume will present a state-of-the art description and analysis of the rapidly expanding field of store-operated Ca^{2+} entry (SOCE). And this first section will deal with the most fundamental mechanistic concepts underlying this process. In this brief introduction, I will try to summarize the historical development of the concept of store-operated Ca^{2+} entry, and say a bit about some recent work that speaks to its general function in cell signaling.

1.1 SOCE: Historical Development of the Concept

Many would attribute the origins of this concept to my 1986 hypothesis paper in Cell Calcium (Putney 1986), but in fact no idea is born in a vacuum and much of the key elements for this concept developed from much earlier findings. One earlier and fundamental concept is that Ca^{2+} signals can arise in two very general ways: either by influx to the cytoplasm across the plasma membrane, or by discharge to the cytoplasm from storage depots within the cell. Although it is now clear that this is a general property of Ca^{2+} signaling pathways, it was the smooth muscle physiologists who first appreciated it, based largely on the differential sensitivity of initial and sustained contractures to removal of extracellular Ca^{2+} (Bohr 1963; Van Breemen 1969; Sitrin and Bohr 1971; Van Breemen et al. 1973; Steinsland et al. 1973; Reviews: Bohr 1973; Bolton 1979). The finding that this same dual mechanism of Ca^{2+} mobilization applied to other, non-excitable cell types led to the suggestion that it was a general property of Ca^{2+} signaling systems (Putney et al. 1981). Commonly both processes occur and they interact and regulate one another in a variety of ways. One clear example is the heart where the influx of Ca^{2+} is

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amplified many fold through a process of Ca^{2+}-induced Ca^{2+} release through ryanodine receptors in the sarcoplasmic reticulum (Meissner 1994). However, the more common mechanism operates in the reverse mode: release of intracellular Ca^{2+} activates Ca^{2+} influx channels in the plasma membrane, which is the process of SOCE, and the focus of this volume.

Early in my career, I attempted to understand Ca^{2+} signaling in exocrine gland cells by monitoring a downstream Ca^{2+}-regulated event, the activation of Ca^{2+}-activated K^+ channels. Membrane permeability to K^+ could be assessed by the rate of efflux of a radioactive K^+ mimic, $^{86}Rb^+$. In a pattern reminiscent of the earlier studies on smooth muscle contraction, activation of any of three surface receptors (muscarinic, α-adrenergic or Substance P) stimulated the rate of $^{86}Rb^+$ efflux and this response occurred in two phases: a transient phase which did not depend upon extracellular Ca^{2+}, and a sustained phase that required extracellular Ca^{2+} (Putney 1976). The nature of the Ca^{2+} independent phase was not known until in a subsequent study, it was shown to depend upon an internal pool of Ca^{2+} that was released in response to receptor activation (Putney 1977). Thus, these three receptors appeared each capable of releasing stored Ca^{2+} and also activating Ca^{2+} influx through plasma membrane channels. Further, by use of a series of experiments employing serial application of different agonists and antagonists under differing conditions, it was shown that a single pool of intracellular Ca^{2+} as well as a single population of surface membrane channels were commonly regulated by the three different receptor types. In the absence of extracellular Ca^{2+}, the released Ca^{2+} was lost from the cells, presumably through active extrusion at the plasma membrane, but could be replenished from the outside, apparently through the receptor-activated channels. This was the first suggestion that plasma membrane channels were responsible for maintaining the intracellular stores, although it was not that clear that this could occur completely independently of receptor activation. That receptor activation was not required to refill the stores was shown by experiments of a similar nature carried out with slices of rat lacrimal gland. In the previous study with parotid slices (Putney 1977), refilling was achieved with the following protocol: in the absence of external Ca^{2+}, stores were emptied with agonist for one receptor (muscarinic), then Ca^{2+} was restored to permit influx, then the agonist was removed pharmacologically by application of a potent receptor antagonist (atropine). Ca^{2+} was then removed, and a second agonist (Substance P) was applied which induced a robust transient $^{86}Rb^+$ efflux, indicative of efficient refilling of the pools. In the subsequent study with lacrimal slices (Parod and Putney 1978), a similar protocol employing epinephrine as the first agonist, phentolamine as the antagonist and carbachol to assess refilling produced essentially the same result as before. However, in this study an alternative sequence was also tested: following depletion of the intracellular store by epinephrine, phentolamine was added before restoration of extracellular Ca^{2+}. In this condition, it was assumed that the receptor-operated channels were inactive. However, a brief (2 min) application of external Ca^{2+}, even after phentolamine, was equally efficient in refilling the intracellular stores. This experiment indicated that refilling could occur efficiently in the absence of receptor activation. Three years later, Casteels and Droogmans (1981) reported a similar phenomenon in smooth muscle. They proposed a privileged route

by which Ca^{2+} could enter the intracellular stores, in this case sarcoplasmic reticulum, without traversing the cytoplasm.

In 1983 came the discovery of the Ca^{2+} mobilizing second messenger, inositol 1,4,5-trisphosphate (IP_3) (Berridge 1983; Streb et al. 1983). The initial experiments involved demonstration of IP_3-induced release from intracellular stores, mainly by use of permeable cell models (Streb et al. 1983; Burgess et al. 1984; Biden et al. 1984) but also with microsomal fractions (Prentki et al. 1984; Streb et al. 1984; Ueda et al. 1986). However, when plasma membrane fractions were separated from endoplasmic reticulum, it appeared that IP_3 did not activate release from the plasma membrane vesicles (Streb et al. 1984; Ueda et al. 1986). Yet, injection of IP_3 into sea urchin oocytes produced a full fertilization response, known to require activation of Ca^{2+} influx (Slack et al. 1986). At this point I attempted to put together the prior work on Ca^{2+} entry with the more recent findings with IP_3 to come up with a model that could account for the biphasic nature of Ca^{2+} signaling. This was the often cited 1986 hypothesis paper published in Cell Calcium (Putney 1986). I chose this instrument, a hypothesis paper, for publishing this idea because at the time I did not know how to proceed to test it. I used the term "capacitative" to describe a mechanism by which the empty state of the intracellular store signaled to and activated Ca^{2+} channels in the plasma membrane. Closely associated components of the endoplasmic reticulum would then rapidly capture this entering Ca^{2+} resulting in efficient refilling of intracellular stores. I envisioned the process of Ca^{2+} entry as a constant refilling of the stores and constant emptying through the IP_3 receptor; thus the analogy with electrical circuitry whereby current flows through a resistor and capacitor in series. This idea was somewhat similar to the model proposed by Casteels and Droogmans (1981), although I assumed a series arrangement of channels and ER pumps, rather than a direct conduit. Subsequent findings confirmed the basic idea of store Ca^{2+} content regulating influx, but the route of entry was not as envisioned by either myself or Casteels and Droogmans. This was clearly demonstrated in two subsequent studies that provided the initial proofs for the concept of store-operate Ca^{2+} entry.

The first was a report in the Biochemical Journal in 1989 in which transient increases in $[Ca^{2+}]_i$ were observed during refilling of intracellular stores, independently of receptor activation (Takemura and Putney 1989). The protocol was similar to the earlier study in lacrimal cells in which stores refilled rapidly following block of the agonist receptor. The major difference was that $[Ca^{2+}]_i$ was more directly monitored by using the newly developed Ca^{2+} indicator, fura-2 (Grynkiewicz et al. 1986). In the earlier study, no increase in $^{86}Rb^+$ efflux was seen during the process of refilling, suggesting a highly protected route to the stores. But with fura-2, one could clearly see a transient rise in $[Ca^{2+}]_i$ during the refilling process. The rise was transient because as the stores refilled, the store-operated process shut down. The second key finding, reported in that same year, served to simplify and redefine the primary experimental paradigm for demonstrating and investigating store-operated Ca^{2+} entry. Thapsigargin is an inflammatory plant toxin that was shown to increase Ca^{2+} in cells (Ali et al. 1985; Thastrup et al. 1987). Jackson et al. demonstrated that thapsigargin released the same pool of Ca^{2+}

as did phospholipase C-linked agonists, but without increasing the formation of IP_3 (Jackson et al. 1988). The mechanism for this release was not known at the time, but was later shown to result from inhibition of the sarcoplasmic-endoplasmic reticulum Ca^{2+} ATPase which is responsible for concentrating Ca^{2+} in the intracellular stores (Thastrup et al. 1990). I recognized that this reagent could serve as a test of the store-operated Ca^{2+} entry idea, but I was discouraged by the fact that Jackson et al. did not apparently observe any increased Ca^{2+} entry in the cells they studied. Nonetheless, there was evidence from the earlier studies in platelets that thapsigargin could cause a sustained $[Ca^{2+}]_i$ increase (Thastrup et al. 1987) and very early experiments examining the effects of Ca^{2+} repletion on secretion provided evidence that thapsigargin likely did augment entry (Patkar et al. 1979). When we applied thapsigargin to parotid acinar cells, a robust and sustained elevation in $[Ca^{2+}]_i$ ensued (Takemura et al. 1989). Removal of external Ca^{2+} and its subsequent restoration clearly demonstrated that this sustained elevation was due to increased Ca^{2+} entry across the plasma membrane. Importantly, thapsigargin and a phospholipase C-linked agonist, methacholine, were not additive in increasing Ca^{2+} influx, indicating that thapsigargin had stimulated the same pathway for Ca^{2+} entry as had the more physiological receptor agonist. Two important implications came from this study. First, it provided direct evidence that simply depleting Ca^{2+} stores could quantitatively account for all of the Ca^{2+} entry produced by activation of the phospholipase C-IP_3 signaling pathway. Second, since IP_3 receptors were not activated, it indicated that the pathway to the cytoplasm did not traverse the IP_3-regulated Ca^{2+} pool but that the Ca^{2+} entered the cytoplasm directly through the store-operated channels (Takemura et al. 1989; Muallem et al. 1990). Why did Jackson et al. not see Ca^{2+} entry in their studies with thapsigargin? We now know that the cell line used in that study, NG115-401L, a neuroblastoma/glioma hybrid line, is deficient in store-operated Ca^{2+} entry (Csutora et al. 2008) due to a deficiency in the Ca^{2+} sensor STIM1. And a third important consequence of the 1989 paper on thapsigargin was that it provided perhaps the simplest and most readily understandable evidence for store-operated Ca^{2+} entry. Interest in this phenomenon increased as a new tool for its investigation became available.

In 1992 a major advance occurred when Hoth and Penner published the first recordings of whole-cell current activated by Ca^{2+} store depletion (Hoth and Penner 1992). They called the current I_{CRAC} for Ca^{2+} release-activated Ca^{2+} current. The current was similar to other selective Ca^{2+} current in being highly selective for Ca^{2+}, and thus strongly inwardly rectifying with a positive reversal potential. The current was small, however, in the range of only a few pA/pF. Actually, in the mast cells which Hoth and Penner used in their initial studies, and other hematopoetic cells, such as T-cells, I_{CRAC} seems to be somewhat larger than other cell types where is may be close to threshold levels of detection, $<$1pA/pF (for example; Vig et al. 2006; DeHaven et al. 2007). And even these small currents are generally only seen when Ca^{2+} inactivation of the current is reduced or prevented, by either inclusion of chelators in the patch pipette solution, or by holding at relatively positive membrane potentials. Hoth and Penner used the whole-cell patch clamp technique to measure

total membrane current; attempts to detect single channels underlying I_{CRAC} were unsuccessful. Subsequently, Zweifach and Lewis (1993) used a noise analysis algorithm to estimate the single channel conductance of CRAC channels to be ~24 fS, well below the level detectable by conventional electrophysiological techniques. Two clues to the molecular nature of the channels were provided in these early studies: first, I_{CRAC} developed rather slowly following store depletion, with a time constant of the order of 20 s; second, the extremely low estimated single channel conductance predicted that the molecular nature of the CRAC channel might be very different from other ion channels.

From 1992 to 2005 research on store-operated Ca^{2+} entry followed three general lines: investigations into the properties and regulatory mechanisms for I_{CRAC} and store-operated Ca^{2+} entry, for example, the complex regulation by intracellular and extracellular Ca^{2+}; attempts to delineate the mechanism by which depleted Ca^{2+} stores signaled to plasma membrane Ca^{2+} channels; attempts to identify the store-operated channels. Whereas the first thread of investigation produced a lot of useful information, the other two sometimes yielded briefly encouraging findings which usually did not survive further scrutiny. Some issues from this earlier work still remain unsettled, for example the role of the hypothetical signaling molecule, Ca^{2+} influx factor (Csutora et al. 2008), and the function of transient receptor potential channels in store-operated Ca^{2+} entry (Liao et al. 2008). These issues have been discussed in a number of exhaustive reviews (Parekh and Penner 1997; Lewis 2001; Putney and McKay 1999; Barritt 1999; Parekh and Putney 2005; Cahalan 2009; Yuan et al. 2009) and will to some extent continue to be addressed in the current volume (see Chaps. 4, 5 and 7).

In 2005 the modern, molecular era of store-operated Ca^{2+} entry began with the initial identification of the endoplasmic reticulum Ca^{2+} sensors, STIM1 and STIM2 (Roos et al. 2005; Liou et al. 2005), followed shortly thereafter by the Ca^{2+} channel proteins, Orai1, 2 and 3 (Feske et al. 2006; Vig et al. 2006; Zhang et al. 2006). Much will be said about these proteins in the following Chaps. 2–4 and in the other Parts 2 and 3 in this volume. Briefly, the STIM proteins are endoplasmic reticulum resident single pass membrane proteins with a Ca^{2+} binding domain directed to the lumen of the endoplasmic reticulum. Upon release of Ca^{2+} from the endoplasmic reticulum, Ca^{2+} dissociates from the domain resulting in a conformational change, association of STIM proteins into dimers and higher order oligomers, and accumulation of STIM at endoplasmic reticulum—plasma membrane junctions where STIM interacts with and activates channels composed of Orai subunits (Hogan et al. 2010; Cahalan 2009; Prakriya 2009; Hewavitharana et al. 2007; Smyth et al. 2006). Note that for some years before the discovery of Orai channels, there was considerable interest in the possible role of TRPC channels as store-operated channels (Parekh and Putney 2005). There remains the possibility that these somewhat less selective cation channels can function in a store-operated mode, and this is an issue that will be addressed in Chaps. 5 and 6, and which has been discussed in recent publications (Yuan et al. 2009; Ambudkar and Ong 2007; Liao et al. 2009).

1.2 The Physiological Function of SOC Channels

The availability of molecular tools to investigate store-operated Ca^{2+} entry has afforded an opportunity to address a long-standing question: what is the physiological function of store-operated Ca^{2+} channels? At the level of the organism, it is clear that this process is very important as mutations in the major players, whether arising by chance in humans, or by design in animal models, in all cases produce severe phenotypes characterized by general immune deficiencies as well as problems in musculo-skeletal development and problems with ectodermally derived tissues and functions (Feske 2009). But what is the basis for these effects at the cellular level? The basic assumption has been that these channels serve to refill and maintain endoplasmic reticulum Ca^{2+} stores, which are important for Ca^{2+} signaling as well as for proper protein synthesis and protein folding. This is no doubt true, but some recent findings have suggested that these channels may have more direct roles in Ca^{2+} signaling. To understand how store-operated Ca^{2+} entry fits into Ca^{2+} signaling pathways, it is necessary to understand the complexity of Ca^{2+} signals when they occur in the physiological range of stimulus strengths. In both excitable cells and non-excitable cells, Ca^{2+} signals most commonly occur as one or a series of regenerative all-or-none bursts of cytoplasmic Ca^{2+} sometimes termed Ca^{2+} oscillations (Woods et al. 1986; Berridge and Galione 1988; Thomas et al. 1996). In excitable cells these often result from the excitable behavior of plasma membrane Na^{+} and Ca^{2+} channels. In non-excitable cells, they generally represent episodic discharges of stored Ca^{2+}. There has been much discussion about the primary source of these intracellular release oscillations. In the vast majority of cases it is clear that they represent episodic release of stored Ca^{2+} by IP_3; however, opinions differ as to whether it is the IP_3 level which is oscillating or whether complex feed forward and feed back mechanisms at the level of the IP_3 receptor can produce oscillations in Ca^{2+} release at a constant IP_3 level (Goldbeter et al. 1990; Meyer and Stryer 1988; Thomas et al. 1996; Dupont et al. 2007). In either case, there is general consensus that the function of these oscillations is to produce a mode of digital Ca^{2+} signaling (Lewis 2003; Dolmetsch et al. 1998). Theoretically, digital Ca^{2+} signaling can be achieved if the immediate downstream response element responds only to a level of $[Ca^{2+}]_i$ above a certain threshold, significantly above the resting $[Ca^{2+}]_i$ level. A series of oscillations can be integrated and thus converted to an analog signal if the time constant of the response element is slow in comparison to the interspike interval of the oscillations. There is evidence that one major response element, a Ca^{2+}-calmodulin dependent protein kinase, does have the appropriate kinetic characteristics to act as an integrator of Ca^{2+} oscillations (De Koninck and Schulman 1998).

So, in order to understand the basic cellular function of store-operated Ca^{2+} channels, one would need to understand their role in the signaling function of Ca^{2+} oscillations. Clearly Ca^{2+} influx plays a role in Ca^{2+} oscillations because removal of external Ca^{2+} causes the oscillations to rapidly run down and eventually cease altogether (Thomas et al. 1996; Bird and Putney 2005). However, in the majority of instances Ca^{2+} entry contributes little if any to the global rise in $[Ca^{2+}]_i$ associated