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Review

Calcium signalling in diabetes

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ABSTRACT

Molecular cascades responsible for Ca^{2+} homeostasis and Ca^{2+} signalling could be assembled in highly plastic toolkits that define physiological adaptation of cells to the environment and which are intimately involved in all types of cellular pathology. Control over Ca^{2+} concentration in different cellular compartments is intimately linked to cell metabolism, because (i) ATP production requires low Ca^{2+}, (ii) Ca^{2+} homeostatic systems consume ATP and (iii) Ca^{2+} signals in mitochondria stimulate ATP synthesis being an essential part of excitation–metabolic coupling. The communication between the ER and mitochondria plays an important role in this metabolic fine tuning. In the insulin resistance state and diabetes this communication has been impaired leading to different disorders, for instance, diminished insulin production by pancreatic β cells, reduced heart and skeletal muscle contractility, reduced NO production by endothelial cells, increased glucose production by liver, increased lipolysis by adipose cells, reduced immune responses, reduced cognitive functions, among others. All these processes eventually trigger degenerative events resulting in overt diabetes due to reduction of pancreatic β cell mass, and different complications of diabetes, such as retinopathy, nephropathy, neuropathy, and different cardiovascular diseases.

1. Molecular physiology of calcium signalling

1a. Historic prelude: calcium ions in life and death

Numerous seminal experiments performed by Sydney Ringer in second half of 19th century established the foundations for physiology and pathophysiology of calcium signalling in living tissues. Ringer has demonstrated that Ca^{2+} ions are indispensable for numerous vital processes being central elements for muscle contraction, fertilization, development and animal survival [1–3]. In 1928, Herbert Pollack for the first time observed intracellular Ca^{2+} dynamics in amoeba injected with alizarin (this dye was used in textile from antiquity and in histology from 1914 for detecting Ca^{2+} salts [4]). Alizarin readily precipitates Ca^{2+} ions and resulting salt appears in the form of purple crystals. Polack observed localized Ca^{2+} elevations; moreover he also found that chelating of Ca^{2+} by alizarin transiently immobilized amoeba indicating physiological role of Ca^{2+} for regulated movements [5].

The pathological role of Ca^{2+} ions that, being in excess, act as universal mediators of cell injury and death, had been recognized in late 1960s (see [6] for review) and in 1974 the key role of excessive plasmalemmal Ca^{2+} entry and subsequent Ca^{2+} overload in triggering ischaemic death of cardiomyocytes was suggested by Albrecht Fleckenstein [7]. Some years later the same massive Ca^{2+} influx was identified as a death signal in ischaemic cerebellar neurones [8], and soon the role of deregulation of Ca^{2+} homeostasis in initiation of numerous death routines has been established [9–11].

1b. Evolutionary routes

Control over intracellular Ca^{2+} concentration is the common feature of all living forms (including humans) in our world. Calcium ion is arguably the most ubiquitous signalling molecule controlling a wide array of cellular functions [12]. Importantly, the cytosolic Ca^{2+} concentration which is kept at very low levels of 50–100 nM against a huge gradient by both passive and active mechanisms; the former involves the activity of different Ca^{2+} buffering proteins while the latter includes the consumption of ATP either directly by Ca^{2+} pumps or indirectly by exchangers. This low cytoplasmic $[Ca^{2+}]$ is critical for cell survival, and loss of tight control over cytosolic Ca^{2+}

Abbreviations: ER, endoplasmic reticulum; NO, nitric oxide; SERCA pump, sarco-endoplasmic reticulum calcium ATPase; UCP, uncoupling protein.

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signals cell death. This is a common feature of all life forms on Earth, which most likely appeared many billions years ago, when protocell emerged in the alkaline prebiotic ocean, in which $[Ca^{2+}]$ were extremely low, in a range of hundreds of nanomoles [13]. It was therefore natural that ancestral cells had a low cytoplasmic $[Ca^{2+}]$, which created favourable conditions for polyphosphates emergence (like nucleotides as ATP, RNA, phospholipid membranes, etc.), and hence Ca^{2+} and ATP become tightly linked as major molecules of life. Slow increase in $[Ca^{2+}]$ in the ocean triggered evolution of Ca^{2+} homeostatic systems, which resisted concentration pressure and actively maintained low cytosolic Ca^{2+}. Activity of this homeostatic system also led to an emergence of steep Ca^{2+} concentration gradients between extracellular space and the cytoplasm, which eventually turned out underlying Ca^{2+} signalling. A large repertoire of proteins evolved as high affinity Ca^{2+} binding molecules. Some of them, while inserted in different membranes, were able to control transmembrane Ca^{2+} movements in the form of Ca^{2+}-permeable channels and Ca^{2+} transporters, and hence the versatile and highly plastic system of Ca^{2+} signalling become operational [14,15].

1c. Molecular principles of Ca^{2+} signalling

Cellular Ca^{2+} homeostasis and adaptive Ca^{2+} signals are controlled by the same molecules which can be broadly classified into Ca^{2+} channels and Ca^{2+} transporters [12,16,17]. The former provide a pathway for Ca^{2+} diffusion through transmembrane aqueous pore; the driving force that defines the direction and intensity of this diffusion is represented by a Ca^{2+} concentration gradient and membrane potential (together form the electro-chemical force). Transporters for Ca^{2+} are represented by Ca^{2+} pumps that directly use ATP energy to transport Ca^{2+} ions against concentration gradient and ion exchangers which use ATP energy indirectly, being driven by electro-chemical transmembrane gradients. The Ca^{2+}-permeable channels are quite diverse and include two families of highly Ca^{2+} selective channels, the voltage-gated Ca^{2+} channels and store-operated Orai channels. Additionally, there are large numbers of non-selective Ca^{2+} permeable channels at both the plasma membrane and intracellular membranes which include ligand-gated channels (also known as neurotransmitter receptors, with all three main types of these receptors, the trimeric purinoceptors, the tetrameric glutamate receptors and some of the pentameric receptors are permeable to Ca^{2+} ions), transient receptor potential channels (TRPs), IP_3Rs, RyRs, mitochondrial uniporter (MCU) and several types of non-selective cation channels. Balance between calcium diffusion through membrane channels and transmembrane Ca^{2+} transport defines Ca^{2+} homeostasis [18].

Both physical (light, heat, stretch, etc.) and chemical (neurotransmitters, hormones, etc.) stimuli lead to rapid and transient changes in Ca^{2+} permeability of plasmalemma and/or intracellular membranes, which results in Ca^{2+} fluxes that alter $[Ca^{2+}]$ within intracellular compartments. These changes in free Ca^{2+} content inside cell are sensed by Ca^{2+}-dependent enzymes that transduce fluctuations in Ca^{2+} concentration into biochemical processes and physiological reactions [18–20]. Importantly, all molecules involved in Ca^{2+} homeostasis and signalling are subject to feedback control by Ca^{2+} ions themselves, which makes the whole system robust and adaptable [21].

2. Pathophysiology of calcium signalling

Deregulation of Ca^{2+} homeostasis accompanies most (if not all) forms of cellular damage and cell death irrespective to aetiology of pathological insult. Indeed, irrespective of the nature of the injury, the cytotoxicity is always accompanied by a sustained and long-lasting elevation in cellular Ca^{2+} content. Increases in intracellular Ca^{2+} are triggered by organic and non-organic substances, from cyanides to mercury; also Ca^{2+} overload accompanies cell death initiated by toxic components arising from virus walls. Similarly, intracellular Ca^{2+} increases and aberrant fluctuations of intracellular $[Ca^{2+}]$ are observed in ischaemic cell death, in glutamate excitotoxicity, in hormonal killing of immunocompetent cells and in complement- or T-cells dependent cytolysis [11]. Conceptually, cell injury almost invariably results in generation of pathological Ca^{2+} signals, which may originate from increased plasmalemmal Ca^{2+} entry, increased Ca^{2+} release from the intracellular stores, reduced cytoplasmic passive Ca^{2+} buffering, compromised Ca^{2+} extrusion or combinations of the above. Whatever the nature of triggering event, the cell overload with Ca^{2+} further compromises ATP production (through generating pathological Ca^{2+} overload of mitochondria), which contributes to further damage to Ca^{2+} homeostatic machinery, these events eventually setting up a vicious circle of positive feedbacks that exacerbate Ca^{2+} overload and lead to irreparable damage. Deregulation of Ca^{2+} homeostasis and cell overload with Ca^{2+} activate multiple intracellular enzymatic cascades, which in turn trigger or execute death subroutines.

Damage to Ca^{2+} homeostatic/signalling machinery also contributes to numerous chronic pathological developments, and which aberrant Ca^{2+} handling does not trigger immediate cell death but rather compromise cellular functions. In neurology, for example, the aberrant Ca^{2+} homeostasis and pathological Ca^{2+} signalling has been implicated in many different diseases such as ischaemia, malignant hyperthermia, major depression, autistic spectrum disorders, epilepsy, migraine and neurodegeneration [22–25]. In these pathologies, slow emerging and long-lasting deterioration of Ca^{2+} homeostatic capabilities contribute to aberrant synaptic transmission or compromise neuronal metabolism.

3. Deregulation of Ca^{2+} homeostasis and Ca^{2+} signalling in diabetes

3a. General pathophysiology of diabetes

Diabetes is a disease characterized by a permanent hyperglycemia due to a diminished insulin secretory activity of pancreatic β cells which in turn is the consequence of direct destruction of β cells or in response to a state of insulin resistance. The former is Diabetes Mellitus type 1 (DM1) while the latter is Diabetes Mellitus type 2 (DM2). These are the two most usual forms of Diabetes and DM2 represents around 90% of all cases of DM. The incidence of DM2 has been on the rise since the 1990s worldwide and diabetes complications are responsible for both morbidity and mortality associated with this illness. This special issue will concentrate on two questions: How is DM developed? Particularly, what is the role of Ca^{2+} and ER stress in the genesis of DM2? And the other question is how complications are developed in DM? Particularly in heart cells because cardiomyopathy is responsible for a large fraction of the mortality associated with DM2 [26–28]. However, it will be reviewed also other complications like neuropathy [29] and endothelium dysfunction [30,31] that could lead to diabetic foot, nephropathy and retinopathy.

It appears that DM2 has a very limited genetic background and it is now considered more a disease of life style since there is no clear gene profile that can explain this disease [32,33]. This conclusion is supported by the presence of homozygous twins discordant for diabetes; this means that genetically identical twins are not necessarily doomed with the disease. Indeed, this study has recognized a considerable non-genetic contribution to glucose metabolic