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A magnificent story in the making...

Andrea Romani

Department of Physiology and Biophysics, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106-4970, USA, amr5@po.cwru.edu

More than 30 years ago Page and Polimeni were the first to determine that cardiac cells regulate their cellular Mg^{2+} content and require more than 72 hours for a physiological turnover of cell Mg^{2+} to occur under nonstimulated conditions [1]. Approximately 10 years later, Gunther and colleagues made the original observation that erythrocytes extrude excess cellular Mg^{2+} magnesium via a Na^+ -dependent mechanism inhibited by amiloride [2]. In 1990, our laboratory provided the first evidence that Mg^{2+} extrusion occurs via a cAMP-mediated process [3] and that a variety of hormones are involved in inducing fast fluxes of Mg^{2+} in both direction across the cell membrane [4]. For the last 20 years, an increasing number of studies have continued to expand these original reports in a broad variety of mammalian cells [see Refs. 4 and 5 for a list]. Aside from a couple of exceptions, the majority of these studies have confirmed the operation of the Na^+/Mg^{2+} exchanger as the main Mg^{2+} extrusion mechanism in mammalian cells. In addition, evidence has been provided for: (1) the presence of a Na^+ -independent Mg^{2+} extrusion mechanism, whose operation is accentuated under conditions in which extracellular Na^+ is not readily available; (2) the presence of Mg^{2+} entry mechanisms, the majority of which appears to operate as a channel; and (3) the regulation of both Na^+ -dependent and Na^+ -independent Mg^{2+} extrusion mechanisms and possibly some of the Mg^{2+} entry pathways by specific hormones (reviewed by Romani in this issue). At the front of this information, the structure of either Mg^{2+} extrusion mechanism still remains undefined, since neither the Na^+ -dependent nor the Na^+ -independent Mg^{2+} transport mechanism has been cloned. In contrast, several potential Mg^{2+} entry mechanisms have been recently identified and cloned. Needless to say, the lack of information about these two Mg^{2+} extrusion mechanisms together with several conceptual and technical limitations [reviewed in 6 and 7] has significantly limited our understanding of Mg^{2+} transport and homeostasis. Yet, the field of Mg^{2+} regulation has successfully moved from descriptive observations to more mechanistic studies, which now provide the necessary background for better understanding the role of Mg^{2+} in various cell functions under physiological and pathological conditions. These studies, conducted in a broad array of experimental conditions and models, both physiological and pathological, indicate that while the bulk of cellular Mg^{2+} is in the form of a complex with ATP (see the article by Gabriel and Günzel in this issue), changes in total and free Mg^{2+} concentration within the cell and organelles are key to regulating a large number of cellular processes. The list of functions regulated directly or indirectly by Mg^{2+} is quite large, as it includes channels in the cell membrane, the endosarcoplasmic reticulum, and the mitochondrion, ATPases in various cell compartments, and more than 300 enzymes (such as mitochondrial dehydrogenases, ERK1/2, adenylyl cyclase [6]) and numerous cell functions (glycolysis and cell cycle, just to mention two of them).

The articles collected in this issue represent the state-of-the-art of the current knowledge of Mg^{2+} homeostasis and function in mammalian cells. Among these articles, the reports by the

Berlin, Mugabwa, and Steele groups address the increasingly evident role of Mg^{2+} in modulating specific monovalent or divalent cation channels in the plasma membrane of smooth muscle cells and cardiac ventricular myocytes, as well, or in the membrane of the sarcoplasmic reticulum. The report by Steele and collaborators, in particular, highlights the fine divider between Mg^{2+} -controlled functions under physiological and pathological conditions, as it evidences how a decrease in cytosolic Mg^{2+} concentration changes ryanodine receptor responsiveness and facilitates the onset of malignant hyperthermia.

The remaining articles collected here, instead, provide a comprehensive vision of some metabolic functions, cycles, and conditions regulated by Mg^{2+} . On one hand, Rubin amply documents how essential Mg^{2+} is in regulating cell cycle and cell progression from G_0 to G_2 stages by modulating cellular uridine phosphorylation, DNA synthesis, and initiation of protein synthesis. On the other hand, the dysregulation of this process results in the inability of the cell to stop its replication, thus opening the way to the undesired progression toward neoplastic growth (see the article by Wolf and collaborators on this point).

Altered cellular Mg^{2+} homeostasis and enzyme regulation are also at the bases of other severe metabolic conditions such as hypertension, inflammation, and diabetes. An increasing number of experimental and clinical observations, in fact, indicate that the circulating levels of inflammatory cells or stress proteins in neutrophils increase markedly under conditions in which cellular or systemic Mg^{2+} is reduced as a result of a deficient diet or an altered regulation of cellular Mg^{2+} homeostasis (see review by Mazur and colleagues). Similarly, the association of Mg^{2+} transport and regulation with glucose transport and utilization and insulin receptor function provides a new starting point for understanding the involvement of Mg^{2+} dysregulation in the onset and progression of diabetes and its complications. In particular, Mg^{2+} appears to play a unifying role in the onset of the “metabolic syndrome” that accompanies type 2 diabetes, as suggested previously by Resnick [8] and reiterated in this issue by his collaborator Barbagallo along with Dominguez.

Hypertension is another pathological condition resulting from the dysregulation of cellular Mg^{2+} homeostasis. In this case, altered Mg^{2+} homeostasis and transport have two main effects: (1) they affect the operation of specific monovalent or divalent cation channels in the plasma membrane of vascular smooth muscle cells, thus resulting in an increased level of intracellular Na^+ or Ca^{2+} ; and (2) they favor the release of specific cytokines and humoral factor by neutrophils and other inflammatory cells that contribute to the onset of hypertension (see Sontia and Touyz’s article for more detail). The decrease in cellular Mg^{2+} observed in hypertension, and other pathological conditions as well, ultimately results in an increased production of reactive oxygen species via mechanisms that are not fully understood.

Taken together, the results reported here suggest that because of the regulatory role of Mg^{2+} in various metabolic and functional events, any alteration of Mg^{2+} transport or homeostasis ultimately compromises cell operation and whole body function.

We have come a long way from the initial observation that cardiac cells have a slow turnover under physiological conditions and erythrocytes can mobilize excess Mg^{2+} via a mechanism operating as a Na^+/Mg^{2+} exchanger. Far from being comprehensive and exhaustive, the results reviewed in this issue provide a more detailed framework for understanding how physiological control of Mg^{2+} homeostasis plays a key role in modulating a broad variety of cell and whole body functions. At the same time, these results increase our awareness of the relevance of Mg^{2+} dysregulation in the onset of major pathological conditions and their short- and long-term complications.

After more than 30 years, Mg^{2+} research still remains a challenging and fascinating field!

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