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Review

Roles of cell volume in molecular and cellular biology

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ABSTRACT

Extracellular tonicity and volume regulation control a great number of molecular and cellular functions including: cell proliferation, apoptosis, migration, hormone and neuromediator release, gene expression, ion channel and transporter activity and metabolism. The aim of this review is to describe these effects and to determine if they are direct or are secondarily the result of the activity of second messengers.

Contents

1. Introduction

The cell volume and its regulation play a role in a great number of molecular and cellular functions (Fig. 1). Beyond the change in extracellular osmolarity, the cell volume is dependent on several parameters including the activity of ion channels and transporters (Wehner et al., 2003). Among these parameters the acute and chronic fluxes of monovalent ions (thick line in Fig. 1) are important regulators of cell volume, which in turn control several molecular and cellular functions. From this point of view, the activity of K^+ and Cl^- channels are, in relationship with other ions and molecules including ATP and Ca^{2+}, a key feature of cell biology. For this reason, we have developed a new hypothesis based on many observations that cell volume controlled by ion fluxes is responsible for several molecular and cellular functions through membrane tension, concentration of several messengers and macromolecular crowding, i.e. the relative concentration of intracellular molecules (Rouzaire-Dubois et al., 2004, 2009). In this review we describe the roles of cell volume in molecular and cell biology and in each case we try to propose a physico-chemical interpretation of these roles.

2. Proliferation

During the cell cycle, cells must double their volume so that daughter cells have the same size that the mother cell. In the 1970's, (Cone, 1971) and (Cone and Cone, 1976) proposed a "unified theory" suggesting that intracellular Na^+ level was of major mitogenic importance. They showed that, in differentiated neurons from the central nervous system of chick embryo spinal cord, DNA synthesis

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[1] Passed away.

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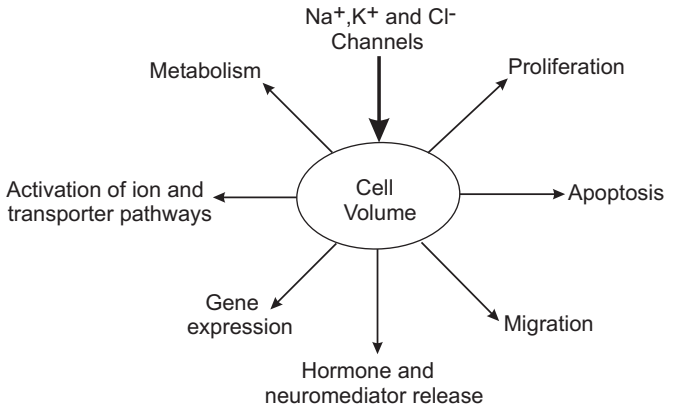

Fig. 1. Schema showing roles of cell volume in molecular and cellular biology.

and mitosis were induced by depolarization with different agents that produce a rise in the intracellular sodium ion concentration and a decrease in the potassium ion concentration. The pharmacological agents used were oubaine, veratridine and gramicidin. These agents induced a 3–20-fold increase in DNA synthesis and mitotic activity. The authors concluded that RNA and DNA synthesis were caused by a significant shift in the intracellular Na^+ level or to the Na^+ to K^+ ratio. They interpreted their results as due to a cell depolarization but did not propose any explanation of how cell depolarization and/or a rise in intracellular Na^+ concentration increase mitosis.

In 1984, De Coursey et al. observed that in human T lymphocytes stimulated by phytohaemagglutinin, which is a potent mitogen for T lymphocytes, the pharmacological blockade of Ca^{2+}-activated and voltage- dependent K^+ channels inhibited in a dose dependent manner both ^{3}H-Thymidine uptake and mitogenesis. While these results were clear the authors did not propose any interpretation of how K^+ channels control mitogenesis.

The fact that K^+ channel blockade inhibited mitogenesis and should have induced a cell depolarization is in apparent contradiction with the results of Cone and Cone (1976) who suggested that cell depolarization increased mitogenesis. However, it should be noted that the experiments of Cone and Cone and De Coursey et al. were made on different preparations namely: mature neurons on one hand and phytohaematogglutinin-stimulated T lymphocytes on the other hand. The opposite effects of cell depolarization can be explained if the relationship between mitosis and some physico-chemical parameters is a bell shape (see below). Later on, the Cones' hypothesis has been abandoned but a great number of reports showed that, in different cell types, the blockade of K^+ channels was associated with an inhibition of mitogenesis and cell proliferation (reviewed by Dubois and Rouzaire-Dubois, 1993; Pardo, 2004; Wonderlin and Strobl, 1996).

Two hypotheses have been proposed to take account of the role of K^+ channels in proliferation. The first one is that cell depolarization reduces the electrochemical gradient and the influx of Ca^{2+} through non-voltage dependent Ca^{2+} channels. This has been demonstrated under voltage-clamp conditions in human melanoma cells (Nilius et al., 1993). Given that Ca^{2+} is necessary for cell division (Munaron, 2002; Santella, 1998) this can explain that a decreased Ca^{2+} influx reduces cell mitosis. However, this interpretation does not take into account all the effects of K^+ channels on cell proliferation. First, tumour cells are almost insensitive to external Ca^{2+} concentration (Rouzaire-Dubois and Dubois, 2004). Second, K^+ channel blockade does not always significantly induce a cell depolarisation whereas it induces an inhibition of cell proliferation (Rouzaire-Dubois and Dubois, 1991). Third, depending on cell types, depolarization can induce either increase or inhibition of mitosis.

More recently, we have proposed a new interpretation on the role on mitosis of ion channels and ion fluxes associated with osmotically water obliged fluxes (Rouzaire-Dubois and Dubois, 1998; Rouzaire-Dubois et al., 2000). According to this hypothesis, the activity of proteins involved in cell cycle progression is dependent on their water environment, which is defined by the macromolecular crowding. On the basis of this theory, we showed on rat glioma cells that an increase in cell volume of small cells increased their rate of proliferation whereas an increase in cell volume from its optimal value decreased their rate of proliferation. In other words, the rate of cell proliferation is a bell shape function of the cell size (Fig. 2). According to Tzur et al. (2009), "the probability of cell division varies independently with cell size and cell age". However in the same article, the authors noted that "the likelihood of division increases with cell size". Moreover, the same authors emphasised that "beyond a critical size cell, the trend is reversed and growth rates decline with increased size". These conclusions are in agreement with our observations (Rouzaire-Dubois et al., 2004) that the rate of cell proliferation is a bell shape function of the cell size.

In conclusion the precise mechanisms by which ion channels regulate proliferation remain an enigma. The "Ca^{2+} theory" has been the object of numerous reports (see Lang et al., 2005) but does not systematically explain the role of Ca^{2+} and depolarization in cell proliferation. In contrast, the "volume theory" that we developed has never been contradicted. In particular, Koegel et al. (2003) showed that the down-regulation of Ca^{2+}-activated K^+ channels in keratinocytes decreased the rate of proliferation and increased the cell size. In view of all these observations, we conclude that the "volume theory" through macromolecular crowding is a better interpretation that the "Ca^{2+} theory" to explain the role of ion channels and ion fluxes in cell proliferation.

3. Apoptosis

Programmed cell death or apoptosis is important in tissue maintenance to compensate for cell proliferation by cell death. Apoptosis is characterised by DNA fragmentation, mitochondrial damage and apoptotic volume decrease (AVD) that result in minimal inflammation to the surrounding tissue. In vitro, apoptosis can be induced by staurosporine that induces a rapid AVD. This cell

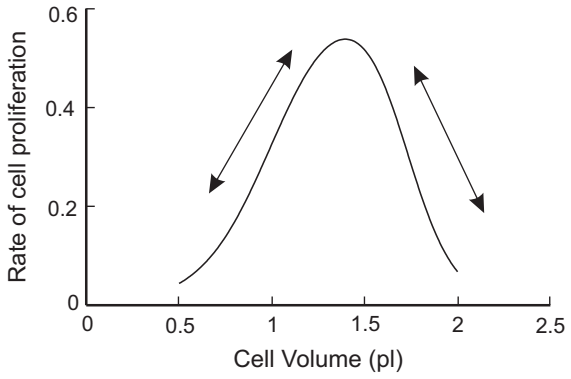

Fig. 2. According to our results on rat glioma cells (Rouzaire-Dubois et al., 2004) the rate of cell proliferation as a function of cell volume can be described by a bell-shaped curve resulting from the combination of two inverse Boltzmann equations. One interpretation of such a curve is that in different cell volume ranges, macromolecular crowding reversibly activates cyclins and cyclin dependent kinase inhibitors.