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What Determines the Intracellular ATP Concentration

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Analysis is made of the mechanisms that control the intracellular ATP level. The balance between energy production and expenditure determines the energy charge of the cell and the ratio of [ATP] to the adenylate pool. The absolute ATP concentration is determined by the adenylate pool, which, in its turn, depends on the balance between the rates of AMP synthesis and degradation. Experimental data are discussed that demonstrate an increase in the adenylate pool in response to activation of energy-consuming processes. A hypothesis is proposed according to which variation in the adenylate pool and absolute ATP concentration affords a cell the possibility of additional control over processes fulfilling useful work. A mechanism involved in this regulation is described using human erythrocytes as an example. The hypothesis explains why different metabolic pathways (protein and DNA syntheses, polysaccharide synthesis, and lipid synthesis) use different trinucleotides (GTP, UTP, and CTP, respectively) as an energy source. This allows the cell to independently control these metabolic processes by varying the individual nucleotide pools.

KEY WORDS: ATP concentration; energy charge; energy metabolism; adenylate pool; adenylate metabolism; pools of cofactors.

INTRODUCTION

ATP plays a paramount role in transferring energy within the cell, diffusing from where it is produced to where it is utilized. Despite numerous studies on ATP metabolism, it remains unclear what determines the intracellular ATP concentration, which varies markedly among tissues of the same species, from species to species [1–9], and during cell differentiation. Intracellular [ATP] decreases severalfold as reticulocytes differentiate to mature erythrocytes [10–12] and increases severalfold as osteoblasts differentiate to osteocytes [13]. The ATP concentration in liver and heart exhibits significant circadian fluctuations [3, 4]. Strikingly, even in normal cells of the same type, [ATP] considerably varies among different individuals. For example, the range of interdonor variation in [ATP] in erythrocytes is greater than twofold [14–17]. Such variations are unlikely to be random. Therefore, the question arises: what determines the intracellular ATP concentration?

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ATP is a component of the intracellular adenylate pool (a), which is a sum of concentrations of all adenylates:

$$a = [ATP] + [ADP] + [AMP] \quad (1)$$

The reversible adenylate kinase reaction

$$2[ADP] \leftrightarrow [ATP] + [AMP]$$

is sufficiently fast in cells to maintain the reactants at their equilibrium concentrations. To have a measure of the content of high-energy phosphate bonds in adenylates, Atkinson has coined the term "energy charge" [18]:

$$\varphi = ([ATP] + 0.5[ADP])/([ATP] + [ADP] + [AMP]) \quad (2)$$

The absolute intracellular ATP concentration depends on the adenylate pool and on the energy charge, that is, on the fraction of ATP in the adenylate pool.

According to the most commonly accepted hypothesis formulated by Atkinson [18], the cell stabilizes its energy charge. The adenylate pool is assumed to follow the changes in the energy charge. When the latter decreases, [AMP] rises, enhancing its own degradation, and thereby stabilizing the energy charge and reducing the adenylate pool size [18].

Ample experimental evidence substantiates Atkinson's hypothesis as far as energy charge stabilization in the cell is concerned. However, when the relationship between the energy charge and the adenylate pool is considered, many experimental results are difficult to reconcile with this hypothesis. Our metabolic studies of erythrocytes have led us to an idea that, when high energy demand is imposed on a cell, a decrease in its energy charge would eventually cause the adenylate pool and absolute ATP concentration to considerably increase (although both parameters may decrease at the initial stages of the response). In this review, we examine how the two hypotheses agree with the available experimental data.

ENERGY METABOLISM

Only two components of the adeylate pool, ATP and ADP, are involved in energy metabolism. It is a well-known experimental fact that the energy charge of most normal cells is close to unity, implying that the adenylate pool size is roughly equal to the ATP concentration [2, 3, 5, 7, 8, 12, 16, 18, 19]. The cell stabilizes its energy charge by adjusting the rate of ATP synthesis to the state of energy demand. A decrease in the energy charge causes the rate of ATP production to rise steeply. Therefore, when ATP-consuming processes are activated to the extent that the energy charge begins to decrease, ATP production is immediately accelerated to cover the increased energy expenditure. Thus, the rate of energy production in the cell is always equal to the rate of energy expenditure. Regulation of ATP production is very efficient and prompt, because the cell produces and expends energy at so high a rate that, when its energy production stops, ATP becomes depleted in just a few minutes [20].

One of the strongest arguments in favor of the view that it is the energy charge that controls the rate of ATP production in the cell has come from studies of energy metabolism in erythrocytes.

Regulation of Energy Metabolism in Erythrocytes

The human erythrocyte is the simplest cell of our organism. Only glycolysis supplies energy to this cell. Theoretical analysis [21–23] predicts that the dependence of the rate of glycolysis on intracellular [ATP] must be a bell-shaped curve (Fig. 1(a)). Let us call this dependence the regulatory characteristic of glycolysis. Its intersection with the rate of ATP consumption vs. [ATP] plot determines the stationary

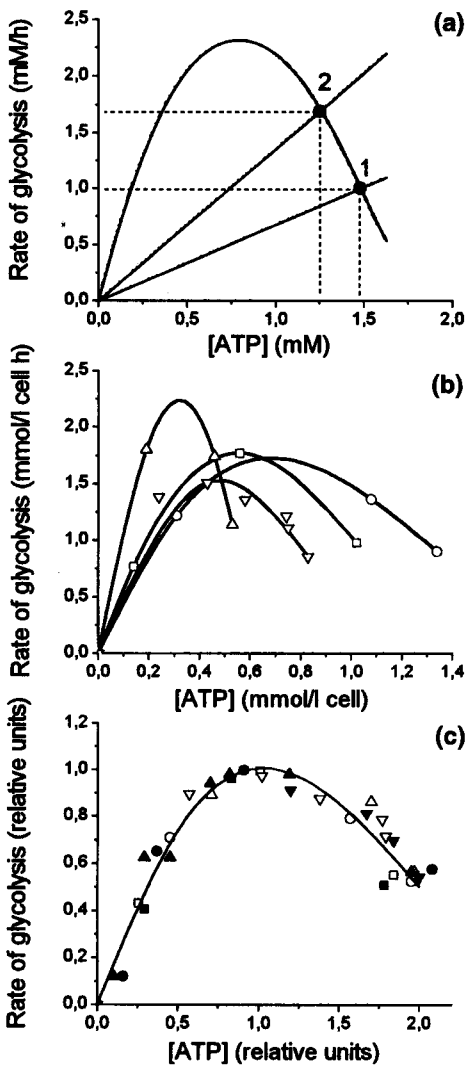

Fig. 1. Regulatory characteristics of energy metabolism in erythrocytes: (a) the rate of glycolysis plotted vs. [ATP], as simulated in the model [24]; (b) experimental curves for the rate of glycolysis as a function of [ATP] in erythrocytes of four different donors; and (c) characteristic of glycolysis in human erythrocytes obtained by normalizing each individual curve to the coordinates of its maximum. In panel (a), sloping straight lines are plots of the rate of ATP consumption vs. [ATP] in (1) control cells and in (2) cells that doubled the ATPase activity in response to stress. The intersection points correspond to the stationary rate of glycolysis and the stationary [ATP] in the cell. As can be seen in this panel, stress that doubles the ATPase activity causes only a 15%-decrease in the [ATP]. For the raw data used in calculating the results sown in panels (b) and (c) see [22]. Different symbols correspond to different donors.

[ATP] value (Fig. 1(a)). The efficiency of [ATP] stabilization against changes in the activity of ATP-consuming processes can be judged by the steepness of the descending part of the regulatory characteristic; its amplitude indicates the permissible range of changes in the rate of ATP consumption in the cell.

Figure 1(b) shows how the rate of glycolysis depended on [ATP] in erythrocytes from four healthy donors. Although the experimental curves of all donors turned out to be qualitatively similar to the theoretical curve, they dramatically differ quantitatively from one another. However, these curves are brought into coincidence by normalizing the rates to their maxima and by plotting the normalized rates vs. the energy charge (or the [ATP]/adenylate pool ratio), rather than vs. the ATP concentration (Fig. 1(c)). The fact that the regulatory characteristics coincide only if they are constructed as functions of the energy charge indicates that the parameter that is mainly stabilized in erythrocytes (and thus is the main regulator of glycolysis) is the energy charge, rather than the absolute ATP concentration. In other words, the regulatory characteristics of erythrocytes constructed as a function of the energy charge are invariant among different individuals. Similar results were obtained on erythrocytes of other species [1].

Mechanism of Regulation of Energy Metabolism

Enzymes cannot "sense" the energy charge: the reactions they catalyze depend on absolute metabolite concentrations. Hence, to be a function of the energy charge, the reaction rate must depend on more than one of the adenylate pool components. For example, the key glycolytic enzyme phosphofructokinase is activated by AMP and inhibited by ATP [20]. When [ATP] and [ADP] vary in erythrocytes, [AMP] also changes, obeying the adenylate kinase equilibrium. Moreover, under physiological conditions, the relative changes in [AMP] are much greater than those that occur in [ATP] [25]. For example, at [ATP] being about 90% of the adenylate pool, a 10%-variation in [ATP] (e.g., from 85% to 95%) results in a more than 8-fold change in [AMP]. What is needed to promptly increase the rate of glycolysis and thereby to restore the energy charge is that a reduction in [ATP] and a rise in [AMP] take place simultaneously. Supposedly, a similar mechanism controls the rate of ATP production via oxidative phosphorylation. In this case, ADP may also act as an effector.

The energy charge is 0.6–0.8 in liver [3–5], 0.7–0.9 in heart [4, 7, 19], and 0.85–0.95 in brain, skeletal muscle and erythrocytes [2, 5, 8, 16, 26–28]. The energy charge exhibits little circadian variation and is relatively stable during physical exercise, starvation, etc. [3, 4, 8, 12, 20, 29]. Unlike intracellular [ATP] in erythrocytes, which varies more than twofold among donors, the energy charge shows little interdonor variation [16, 26, 30].

Hence, energy metabolism is regulated to stabilize the energy charge and the fraction of ATP in the adenylate pool. Obviously, variations in the [ATP] among different cells and tissues and variations in the [ATP] in a given cell type within the species depend only on variations in the adenylate pool size.

Let us now examine in more detail the processes that determine the pool size (and, hence, the absolute ATP concentration) in the cell.

REACTIONS IRREVERSIBLY ALTERING THE CONCENTRATIONS OF THE ADENYLATE POOL COMPONENTS

Utilizing ATP to synthesize of RNA, adenosylmethionine, and many other molecules, the cell irreversibly removes ATP from energy turnover. Therefore, *de novo* ATP synthesis is required to keep its concentration constant. The need to expend adenylates for other syntheses is quite understandable. However, some reactions degrade ATP without synthesizing any useful products. One of them is the AMP deaminase reaction, in which the amino group is irreversibly cleaved from AMP, yielding inosine 5′-monophosphate and ammonia. As AMP is expended in this reaction, the ATP and ADP concentrations decrease because of the adenylate kinase equilibrium. Adenylate synthesis and degradation not related to performing any known functions proceeds in all cells, including erythrocytes, in which AMP deaminase is among the most active enzymes [31].

In view of this fact, it is natural to suggest that cells need highly active AMP deaminase to additionally stabilize their energy charge [18]. If the energy charge decreases for some reason, the AMP concentration rises. AMP deaminase degrades AMP, thereby increasing the energy charge. The stabilizing effect is evident, but the price for this additional stabilization is a reduction in the adenylate pool size and in the absolute ATP concentration. Actually, it is usual that the adenylate pool size decreases following a decrease in the energy charge. In all such cases, ATP is in short supply (as in hypoxia, at low concentrations of substrates for energy metabolism, etc.) and energy requirements of the cell cannot be met [8, 30, 32, 33]. Nonetheless, there is convincing but circumstantial evidence suggesting that activation of ATP-consuming processes in the cell may cause the energy charge to decrease while increasing the adenylate pool size and [ATP]. Increased values of both [ATP] and the adenylate pool were observed in actively growing and reproducing microorganisms [32], in muscles of hibernating animals after their reactivation [27, 28], and in osteoblasts in which differentiation to osteocytes enhances their metabolic activity [13]. In contrast, a decline in energy requirements as in reticulocytes maturing to erythrocytes is associated with a dramatic decrease in the [ATP] and the adenylate pool size [10–12]. Both the adenylate pool and [ATP] in erythrocytes are significantly increased in a number of pathologies, including leukemia [34, 35], sepsis [36], tuberculosis [37], meningococcal infection [38, 39], renal insufficiency [15, 16, 40, 41], and psoriasis [42]. It is conceivable that all these pathologies upset the ion balance between the cell and its environment, activating transport ATPases. Their activation in erythrocytes imposes stress on energy metabolism of these cells. Interestingly, there are data indicating that ion transport across the cell membrane is impaired and $[Na^+]$ in erythrocytes is elevated in renal insufficiency, sepsis, and leukemia [15, 36, 43–45]. Certainly, adenylate pool expansion can be caused by some other reason specific to each particular pathology. However, it seems unlikely that the same effect (adenylate pool expansion) has different causes in different pathologies. Very interesting data has been published on hereditary stomatocytosis [46–48]. The only abnormality found in this pathology is an increase in the cell membrane permeability to Na^+ and K^+ [49]. Analyzing these data, we found a very good positive correlation between cell membrane permeability, ATPase activation, and [ATP] in erythrocytes

Table 1. Cell Membrane Permeability to Na^+ and K^+, the Rate of Ion Pumping, and ATP Concentration in Erythrocytes of Patients with Hereditary Stomatocytosis (Normalized to the Respective Mean for Healthy Donor Erythrocytes)

Membrane permeability		Rate of ion pumping			
Na	K	Na	K	[ATP]	Reference
—	3.7	—	2.0	1.05	[46]
7.8	3.3	4.1	2.2	1.24	[46]
6.0	4.5	4.7	2.2	1.31	[46]
116.9	32.5	12.4	11.5	1.76	[46]
26.7	41.3	15.4	18.1	1.39	[47]
103.2	32.3	39.5	8.6	5.00	[48]

(Table 1). This correlation strongly suggests that activation of the ion pump (which imposes additional energy demand on the erythrocyte) leads to a significant increase (rather than a decrease) in intracellular [ATP].

Thus, the experimental data provide evidence that a reduction in the energy charge does not necessarily imply a concomitant reduction in the size of the adenylate pool; its expansion may also be observed. Studies of how adenylate metabolism is regulated in erythrocytes have led us to a hypothesis that reconciles this discrepancy. By this hypothesis, the adenylate pool size decreases with the decreasing energy charge when energy requirements of the cell exceed its energy-producing capacities, causing a dramatic rise in [AMP], which remains high for a long time. This occurs when ATP synthesis is inhibited, or when ATP-consuming processes become overactivated. When their activation is not too high, the adenylate pool size (and [ATP]) increases in response to a reduction in the energy charge. We suppose that such a response is a better strategy to adopt by cell homeostasis than the strategy ensuing from Atkinson's hypothesis. A rise in ATP in response to increased energy demand is a better way to meet this demand. In our hypothesis, a signal indicating a condition of increased energy demand is a decrease in the energy charge. This signal switches the regulation of the enzymes forming the fluxes of AMP synthesis and degradation. Below, we describe in more detail how AMP metabolism is regulated in erythrocytes according to our hypothesis.

Adenylate Metabolism in Human Erythrocytes

In erythrocytes, the adenylate pool size depends mainly on the balance between AMP synthesis and degradation. AMP is related to the other pool components (ATP and ADP) via the adenylate kinase reaction. There are two pathways whereby AMP is synthesized in erythrocytes (from adenine and adenosine, respectively); and two pathways whereby it is degraded, one catalyzed by AMP deaminase and the other by purine-5′-nucleosidase (AMP phosphatase) [50]. Analysis by mathematical modeling shows that, to have the adenylate pool growing in response to a decrease in the energy charge, it is sufficient to regulate the rate of AMP destruction while the rate of AMP synthesis may remain unchanged. The required regulation of the rate of

AMP destruction, in its turn, may be obtained when it is directly proportional to [ATP] and inversely proportional to [AMP] (i.e., when ATP activates and AMP inhibits AMP destruction) [51, 52]. AMP deaminase exhibits strong positive cooperativity for AMP and seems to be almost inactive at normal intracellular AMP concentrations. Therefore, we suppose that it is AMP phosphatase that controls AMP degradation under physiological conditions [24] (Fig. 2). The role of AMP

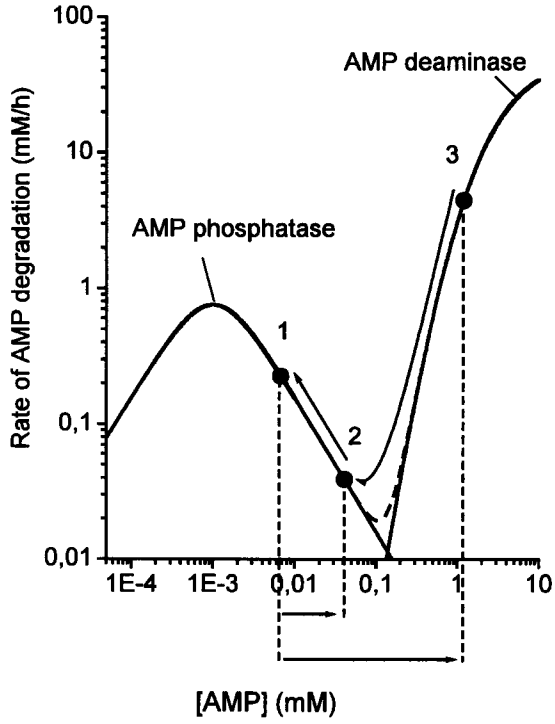

Fig. 2. Graphic illustration of the involvement of AMP phosphatase and AMP deaminase in regulation of the adenylate pool in human erythrocytes: the rates of adenylate degradation by AMP phosphatase and by AMP deaminase vs. [AMP] as simulated in the model [24]. Point 1 corresponds to the normal physiological state of the cell. In response to moderate activation of ATP-consuming processes, the energy charge decreases, but [AMP] rises only slightly (point 2). The degradation of the adenylate pool becomes slower, and its size increases. When the energy charge drops considerably, the rise in [AMP] is great (point 3). The rate of AMP deaminase increases, causing the [AMP] and the adenylate pool to rapidly fall. As a result, the rate of AMP degradation decreases below its initial level, and the adenylate pool begins to grow. It grows up until the energy charge reaches its normal value. By that time, the adenylate pool becomes larger than it has been initially [51, 52].

deaminase comes down to keeping the [AMP] within the limits where it acts as an effector of AMP phosphatase.

Under these assumptions, an abrupt rise in energy demand causes the adenylate pool to respond first by a decrease and then by an increase in its size. The phase of pool decline may be skipped if the ATP-consuming processes are activated moderately. Analysis of mathematical models shows that cell metabolism is stable only if the rate of adenylate metabolism is much lower than the rate of energy metabolism [51]. It is the case for erythrocytes. The rate of adenylate turnover in these cells is tens of micromoles per hour per liter cells [53]. The rate of glycolysis is some 100 times greater. Therefore, natural regulation of the adenylate pool is difficult to study *in vitro*.

A rise in ATP would help a cell to tolerate a state of increased energy demand only if the rate of processes fulfilling useful work were dependent on the ATP concentration, increasing with its rise. For example, ATP in erythrocytes supplies energy mainly to Na, K-ATPase whose activity is responsible for maintaining cation gradients across the membrane. In this way the rate of Na, K-ATPase in the erythrocyte should rise proportionally to the increase in intracellular [ATP]. There is no consensus in the literature concerning the dependence of this ATPase on [ATP]. In numerous studies performed on isolated enzyme or reconstructed transport systems, the Michaelis constant for ATP was found to be quite low, implying a weak dependence of transport ATPase on [ATP] [54, 55]. However, there are serious arguments supporting the notion that in intact erythrocytes the rate of operation of the transport Na, K-ATPase strongly depends on [ATP] [26, 56, 57].

Thus, in our hypothesis, ATP variations in the cell are not random; they are part of stress responses of the cell. The hypothesis explains why intracellular [ATP] is higher in some pathologies than in the norm and why it can increase with the increasing energy requirement. Conceivably, the observed interdonor variations [ATP] in erythrocytes reflect the compensatory responses of these cells to changes in the permeability of their membranes induced by oxidative stresses.

In our hypothesis, the adenylate pool and the intracellular [ATP] are regulated solely via the AMP degradation mechanism, which accounts for the role of "nuisance" enzymes, AMP phosphatase and especially AMP deaminase. Perhaps, no more than this simple hypothesis is needed to describe the situation in erythrocytes. In other cells, this regulation may be more intricate, involving reactions of both AMP degradation and synthesis. However, the main idea remains the same: the adenylate expands with the increase in energy demand imposed on the cell, and *vice versa*.

REGULATION OF THE CONCENTRATIONS OF OTHER COFACTORS

Our hypothesis explains one more property of energy metabolism in animal cells. It is common knowledge that various metabolic systems use different nucleoside triphosphates. GTP plays a role in protein synthesis and intracellular signal transduction, UTP in polysaccharide synthesis, and CTP in lipid synthesis. In all cases, the energy charge is the same. It seems logical to suggest that the pool of each of them is regulated by its own control system adjusted to the requirements of the

metabolic system that uses that nucleoside triphosphate. This allows a cell to independently regulate different metabolic systems (or their large associations).

Figure 3 sums up the results of the analysis described above. At a rate determined by the adenylate energy charge of a cell, its energy machinery (mitochondria or glycolysis) converts ADP to ATP, while other dinucleotides are phosphorylated in fast equilibrium transphosphorylation reactions. As a result, mono-, di-, and trinucleotides are rapidly redistributed according to the energy charge, which is the same for each nucleotide. Its value is determined by the balance between the generalized energy source in the cell and the generalized energy consumer (a sum of all processes expending nucleotides of any type). Note that the absolute concentration of any individual nucleotide does not depend on the cell energetics. Thus, all energy-dependent processes in the cell take place at equal relative concentrations (energy charges) of trinucleotides, and the individual nucleotide pools (absolute concentrations) are independently regulated in a way adjusted to the requirements of their respective metabolic systems.

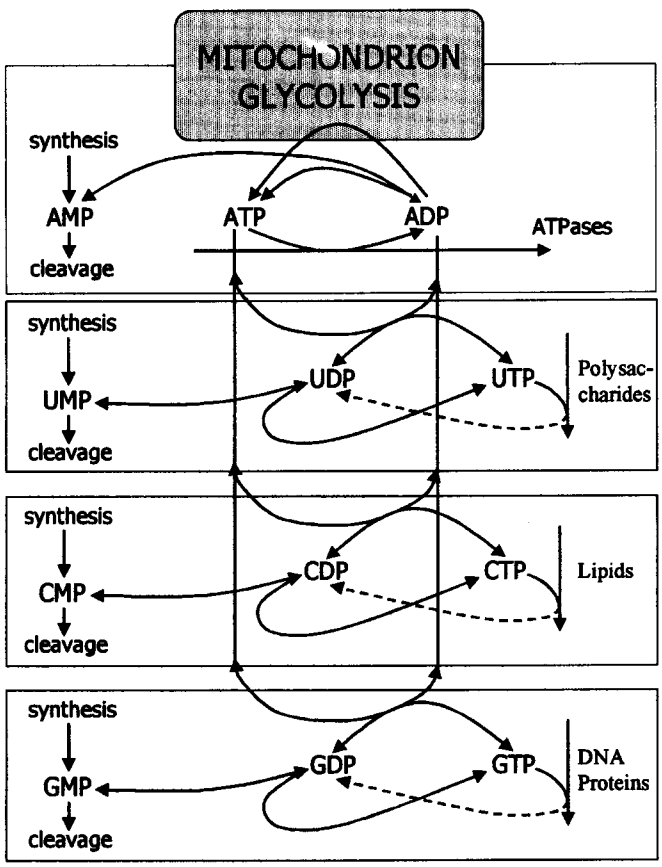

Fig. 3. Scheme of interaction between ATP generation and energy-consuming processes using different trinucleotides.

This hypothesis can be expanded to other cofactors. For example, in redox metabolism, the redox potential and the GSH concentration may play roles similar to those that the energy charge and the ATP concentration, respectively, play in energy metabolism. There are experimental data indicating that oxidant treatment causes a drop in the redox potential, GSH concentration, and the glutathione pool. This drop in the GSH concentration, and the glutathione pool is followed by their growth over a period of several hours to values significantly exceeding the initial ones [58–60]. In contrast, in the presence of antioxidants, both the GSH concentration and the glutathione pool significantly decrease [60].

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