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ATP Cellotoxicity, ATP-Induced Cell Death and ATP Depletion

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ABSTRACT

This paper delves into three pivotal themes concerning adenosine triphosphate (ATP): ATP cytotoxicity, ATP-induced cell death, and ATP depletion. Initially, we scrutinize ATP's involvement in cytotoxicity, with a specific focus on elucidating the mechanisms underlying cell demise triggered by augmented extracellular ATP concentrations. Subsequently, we investigate the process of ATP-induced cell death, emphasizing the repercussions of heightened extracellular ATP levels on cellular dynamics and associated biological responses. Lastly, we probe the impact of ATP depletion on cellular function and contemplate the plausible manifestation of cell death resulting from ATP depletion. Through a comprehensive examination of these topics, a deeper understanding of ATP's multifaceted role in cellular biology emerges, offering novel insights and strategies for the treatment and prevention of related diseases.

KEYWORDS

ATP cytotoxicity; ATP-induced cell death; ATP depletion; Cellular biology

1. ATP CYTOTOXICITY DEFINITION

Adenosine triphosphate (ATP) cytotoxicity denotes the induction of cellular demise under conditions of elevated intracellular ATP concentrations. Typically, ATP serves as a vital energy currency within cells, yet heightened ATP levels may disrupt cellular metabolism, induce oxidative stress, and perturb intracellular calcium ion homeostasis, thereby instigating pathways of cell death including apoptosis or necrosis.

2. ATP-INDUCED CELL DEATH

ATP-induced cell death typically manifests as apoptosis, although a portion also exhibits another form of cell demise, namely necrosis. ATP serves pivotal roles within the cellular milieu, encompassing energy transference, signal transduction, and cellular metabolism. Intracellular ATP levels are intricately maintained through a balance between synthesis and utilization, termed ATP homeostasis. Yet, in response to external cues or internal trauma, this equilibrium may be disrupted, culminating in elevated extracellular ATP levels and intracellular release. Consequently, ATP-induced cell demise occurs. Four primary mechanisms and regulatory pathways may underlie ATP-induced cell death. Firstly, ATP can bind to extracellular purinergic receptors 2 (P2Rs), notably the

P2X7 receptor, concurrently activating associated receptors like NLRP1 and NLRP3. This activation initiates apoptotic signaling involving caspase-1, caspase-3, and caspase-11, and necrotic proteins such as GSDME and GSDMD. Secondly, ATP binding to ion channels on the cell membrane regulates ion balance, activating P2Rs, especially P2X7R, causing ion channel opening and intracellular Ca^{2+} concentration elevation. This leads to nuclear DNA damage and subsequent cell death. Additionally, ATP can induce mitochondrial membrane potential alterations, disrupt the respiratory chain, generate reactive oxygen species (ROS), and modify membrane permeability, culminating in cell demise. Lastly, ATP participates in immune inflammation initiation, cell death activation, and ATP-induced cell death, resulting in inflammatory mediator release and ultimately cell death [1-4].

3. ATP DEPLETION

ATP depletion occurs when there is an inadequate amount of intracellular ATP, resulting in a shortage of cellular energy. Consequently, this insufficiency leads to aberrant cellular function, metabolic dysregulation, and ultimately cell death. Typically, ATP depletion is observed in cells experiencing severe injury, hypoxia, nutritional deficiencies, or other stressful conditions.

4. UNSOLVED MYSTERY

The intricate interplay among ATP cytotoxicity, ATP-induced cell death, and ATP depletion, along with their impact on cell survival, presents an unresolved puzzle in cell biology. This puzzle encompasses a sophisticated regulatory network governing intracellular energy equilibrium, survival mechanisms, and cell death pathways. Despite their interconnections, the precise mechanisms of interaction remain elusive. For instance, it remains uncertain whether ATP depletion directly precipitates cell demise or if ATP cytotoxicity triggers ATP depletion. Whether ATP cytotoxicity induces ATP depletion or vice versa, contributing to cell demise under external stimuli or internal damage, remains unanswered. These phenomena entail intricate regulatory networks involving intracellular signaling, metabolic pathways, and cell death mechanisms, yet their specific intricacies remain incompletely understood. Additionally, factors beyond external stimuli and internal damage that influence the onset and progression of these phenomena warrant further investigation and exploration.

5. REPORTS ON ATP CYTOTOXICITY

The intracellular concentration of ATP, typically in the millimolar range (mean 4.41 mM), is a ubiquitous characteristic observed across various life forms, spanning from prokaryotic to eukaryotic cells [5]. Cells that exhibit resistance to external stressors often display distinctive features, including impaired mitochondrial ATP synthesis, heightened aerobic glycolysis, elevated absolute levels of intracellular ATP, and augmented signaling mediated by HIF-1α. Intriguingly, the direct administration of ATP into resistant cells disrupts the stability of HIF-1α and suppresses glycolytic activity. Consequently, these resilient cells manifest a pronounced "ATP debt," denoting the additional ATP required to maintain homeostasis of survival pathways under genotoxic stress. Notably, the direct provision of ATP is adequate to induce resistance in drug-sensitive cells. Conversely, treatment with the glycolysis inhibitor 3-bromopyruvate depletes ATP levels sufficiently to confer cross-resistance to multiple chemotherapeutic agents [6]. Analysis of the cellular AXP pool under conditions of high osmotic pressure has unveiled an increase in ATP levels while maintaining a constant energy charge. This augmentation of the ATP pool aligns with a substantial rise in the rate of ATP synthesis (qATP), surpassing the anticipated demand associated with regulatory volume

expansion. Hence, the escalation in qATP reflects the heightened energy requirements of cells undergoing hypertonic stress adaptation [7].

6. REPORTS ON ATP-INDUCED CELL DEATH

The activation of the P2X7 receptor by ATP induces apoptosis and autophagy in human epithelial cells, possibly mediated through the generation of reactive oxygen species (ROS), with potential implications for intestinal inflammation [8]. Stimulation of the metabolic ATP receptor (P2Y) promptly elevates intracellular Ca^{2+} levels ([Ca^{2+}]i) in t-bbec117 cells. This rise in [Ca^{2+}]i triggers membrane hyperpolarization and enhances cell proliferation by activating Apapin-sensitive small conductance Ca^{2+}-activated K^{+} channels (SK2). Approximately 15% of t-BBEC 117 cells exhibit a sustained response to ATP for more than 10 minutes, characterized by aberrant membrane hyperpolarization, wherein the inward rectified K+ channel (Kir2.1) is widely expressed. The abnormal hyperpolarization induced by ATP is resistant to removal by vitamin A but sensitive to Ba^{2+}. Prolonged exposure to ATP-γs leads to a relative increase in t-BBEC 117 cells, accompanied by a significant upregulation in Kir2.1 mRNA expression and the persistence of abnormal hyperpolarization with sensitivity to Ba^{2+} [9]. Panx1, a prominent member of the pannexin family, is detectable in both helper (CD4+) and cytotoxic (CD8+) T cells, while Panx2 is expressed at low levels in both T cell subsets. Pharmacological and genetic investigations have revealed that the Panx1 channel predominantly mediates ATP-induced ethidium uptake, as evidenced by the substantial reduction in this uptake upon treatment with Panx1 channel blockers (10Panx1, Probenecid, and low-concentration carbenoxolone), a phenomenon absent in Panx1 - / - murine-derived T cells [10].

7. REPORTS ON ATP DEPLETION

In HeLa cells, the complete blockade of oxidative phosphorylation by oligomycin, myxothiazole, or FCCP, combined with partial inhibition of glycolysis by dogs, resulted in a sustained three-fold decrease in intracellular ATP levels. However, when the dog-containing medium was replaced with a high-glucose medium, ATP levels recovered. Within 48 hours following a brief (3h) reduction and subsequent recovery of ATP levels, most cells undergo apoptosis. If DOG or oxidative phosphorylation inhibitors are administered individually, causing a 10-35% reduction in [ATP], cell death does not ensue. Apoptosis is characterized by the translocation of Bax into mitochondria, the release of cytochrome c into the cytoplasm, caspase activation, reactive oxygen species (ROS) production, and chromatin reorganization and fragmentation [11]. The fibroblasts of the patient accumulated substantial amounts of cystine and exhibited a significant decrease in intracellular ATP content. Remarkably, the overall energy production capacity, activity of respiratory chain complexes, NA-reflecting wachroin-dependent rubidium uptake, K-ATPase activity, and bradykinin-stimulated mitochondrial ATP production remained normal in these cells [12].

8. CONCLUSIONS

This research delves into the ramifications of ATP cytotoxicity, ATP-induced apoptosis, and ATP depletion on cellular physiology. While ATP serves a crucial biological role within cells, an excess of ATP can precipitate cytotoxicity, potentially culminating in cellular demise. Moreover, ATP depletion has the potential to impede cellular function, thereby influencing cellular metabolism and viability.

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