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Autophagy unraveled: Navigating cell fate and disease dynamics

Autophagy is a crucial cellular process involved in the degradation and recycling of damaged cellular components, playing a pivotal role in maintaining cellular homeostasis [1]. The regulation of autophagy significantly influences cell fate decisions, impacting various diseases, including cancer, neurodegenerative disorders, and metabolic conditions [2]. In the context of cancer, autophagy can act as a double-edged sword. It can suppress tumor initiation by removing damaged organelles and proteins, thereby maintaining cellular integrity. However, once a tumor is established, cancer cells can hijack autophagy to survive under stress conditions such as hypoxia and nutrient deprivation. This adaptive mechanism allows tumor cells to resist chemotherapy and other treatments, complicating therapeutic strategies. Recent studies have highlighted the role of specific autophagy-related genes and signaling pathways, such as the PI3K/Akt/mTOR pathway, in modulating autophagic activity and influencing cancer cell survival and death [3,4]. In neurodegenerative diseases, dysregulated autophagy contributes to the accumulation of misfolded proteins and damaged organelles, exacerbating disease progression. Enhancing autophagic activity has been proposed as a therapeutic approach to clear toxic protein aggregates in conditions like Alzheimer's and Parkinson's disease [5,6]. Studies have shown that upregulating autophagy can mitigate the toxic effects of protein aggregates, potentially slowing disease progression [7,8]. Autophagy also plays a crucial role in metabolic diseases such as diabetes and obesity. It regulates lipid metabolism and insulin sensitivity, influencing the development and progression of these conditions. Targeting autophagy through dietary interventions or pharmacological agents offers a promising strategy for managing metabolic disorders by improving cellular metabolism and reducing inflammatory responses [9]. For better understanding the complex regulatory mechanisms of autophagy in cell biology, we organized a special volume in Biochemistry and Biophysics Reports entitled "Regulation of Autophagy in cell fate and disease". The volume covered a wide range of articles focusing on the impact of autophagy in different diseases models.

Shin et al. explores how desipramine, a tricyclic antidepressant, offers protective benefits to rat liver cells under ischemia/reperfusion (I/R) conditions [10]. The researchers investigate the protective effects of desipramine, a tricyclic antidepressant, on rat liver cells under ischemia/reperfusion (I/R) conditions. The study focuses on how desipramine influences autophagy and apoptosis to mitigate cell injury caused by I/R. Ischemia/reperfusion injury typically results in significant cellular damage due to oxidative stress, leading to apoptosis and necrosis. The researchers subjected rat hepatocytes to simulated I/R and administered desipramine to evaluate its cytoprotective potential. The findings revealed that desipramine significantly improved hepatocyte viability during I/R injury. One of the key mechanisms identified was the inhibition of acid sphingomyelinase (ASM) by desipramine. ASM is an enzyme responsible for breaking down sphingomyelin into ceramide, a lipid molecule that accumulates during ischemic conditions and triggers cell death pathways. By inhibiting ASM activity, desipramine reduced ceramide levels, thereby mitigating the initiation of apoptosis. Additionally, the study highlighted the antioxidant properties of desipramine. The treatment with desipramine resulted in decreased markers of oxidative stress and a reduction in reactive oxygen species (ROS) generation. This decrease in oxidative stress contributed to lower levels of apoptosis in hepatocytes. Specifically, desipramine treatment led to a reduction in the activation of caspases, which are enzymes crucial for the execution of apoptosis. The inhibition of these caspases indicated a lower rate of programmed cell death. The study also explored the role of autophagy in desipramine-mediated cytoprotection. Autophagy was modulated by desipramine treatment. The researchers observed an increase in autophagic activity, which helped in maintaining cellular homeostasis and promoting cell survival under I/R conditions. In summary, the manuscript demonstrates that desipramine exerts its cytoprotective effects in rat hepatocytes under I/R conditions by inhibiting ASM, reducing ceramide accumulation, decreasing oxidative stress, and modulating autophagy and apoptosis. These findings suggest that desipramine holds potential as a therapeutic agent for protecting liver cells from I/R injury, warranting further investigation into its clinical applications in hepatic protection.

Transitioning from hepatic cytoprotection to pulmonary hypertension, Hinton et al. explores the effects of mechanical stress on pulmonary hypertension (PH) through a novel model simulating the pulsatile stretch experienced by the vascular walls [11]. The study emphasizes the roles of the unfolded protein response (UPR) and autophagy in response to mechanical stress. Researchers observed that pulsatile stretch significantly activated UPR pathways in pulmonary vascular cells, with increased expression of markers like GRP78, CHOP, and spliced XBP1, indicating elevated ER stress. This activation suggests that mechanical stress contributes to the maladaptive cellular responses in PH, promoting apoptosis and inflammation, key features of vascular remodeling. In addition to UPR, the study also highlighted the role of autophagy under mechanical stress conditions. The pulsatile stretch induced autophagic activity, as evidenced by the upregulation of autophagy-related proteins such as LC3-II and Beclin-1. This response indicates that autophagy may act as a protective mechanism against cellular stress induced by mechanical forces in the pulmonary hypertensive environment. Overall, the findings suggest that both UPR and autophagy are critical responses to mechanical stress in the vascular walls of pulmonary hypertension. These processes contribute to the pathophysiology of PH by promoting cellular survival and adaptation,

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yet they also have the potential to lead to detrimental effects if dysregulated. Targeting these pathways might offer new therapeutic strategies to manage pulmonary hypertension and its associated vascular remodeling.

Moving into the realm of oncology, the article Pandey et al. delves into the intricate relationship between autophagy and the metabolic processes within cancer cells [12]. The authors highlighted autophagy as a critical mechanism that cancer cells exploit to meet their high metabolic demands and survive under stressful conditions, such as nutrient deprivation and hypoxia. The manuscript outlines how autophagy supports cancer cell metabolism by breaking down cellular components to provide essential metabolites and energy. This process aids in maintaining cellular homeostasis and supports the rapid proliferation of cancer cells. Key metabolic pathways, including glycolysis and oxidative phosphorylation, are modulated by autophagy, ensuring that cancer cells have a continuous supply of ATP and biosynthetic precursors. Furthermore, the article discusses the dual role of autophagy in cancer, acting both as a tumor suppressor in normal cells by preventing the accumulation of damaged organelles and proteins, and as a tumor promoter in established cancers by enabling cell survival and growth. The regulation of autophagy by various oncogenes and tumor suppressor genes, such as mTOR, p53, and AMPK, is also explored, highlighting the complexity of its role in cancer metabolism. The authors emphasize potential therapeutic strategies that target autophagy to disrupt cancer metabolism. Inhibiting autophagy could sensitize cancer cells to chemotherapy and radiation, while promoting autophagy in combination with other treatments could overcome resistance mechanisms. The manuscript concludes that a deeper understanding of the context-dependent role of autophagy in cancer could lead to more effective treatments and improved patient outcomes.

Shifting focus to nephrology Kimura et al. investigates the protective effects of fenofibrate against cisplatin-induced nephrotoxicity [13]. Cisplatin is a widely used chemotherapy drug known for its nephrotoxic side effects, which limit its clinical use. The study focuses on the mechanisms through which fenofibrate, a peroxisome proliferator-activated receptor-alpha (PPAR-α) agonist, mitigates cisplatin-induced apoptosis in renal proximal tubular cells. The researchers found that fenofibrate significantly reduces apoptosis induced by cisplatin by inhibiting the p53/Puma/Caspase-9 pathway and the MAPK/Caspase-8 pathway. These pathways are crucial in mediating the apoptotic response to cisplatin, with p53 activation leading to the transcription of pro-apoptotic genes such as Puma, which in turn activates caspase-9. Similarly, the MAPK pathway activates caspase-8, another key player in apoptosis. Interestingly, the study highlights that fenofibrate's protective effects are not due to the promotion of autophagy. Autophagy's effects on cell survival or death, depending on the cellular condition and level of stress. While previous studies have suggested that autophagy might protect against cisplatin-induced nephrotoxicity, this study demonstrates that fenofibrate reduces apoptosis through direct inhibition of apoptotic pathways rather than enhancing autophagic activity. These findings suggest that fenofibrate may offer a therapeutic approach to reduce cisplatin-induced kidney damage by targeting specific apoptotic pathways. This could improve the safety profile of cisplatin in chemotherapy, potentially allowing higher doses to be used or reducing the incidence of nephrotoxic side effects in patients undergoing treatment. The article underscores the importance of understanding the molecular mechanisms underlying drug-induced nephrotoxicity and highlights the potential of fenofibrate as a nephroprotective agent in clinical settings.

In the context of infectious diseases Behrouj et al. discusses how epigenetic modifications influence autophagy during SARS COV-2 infection [14]. Autophagy plays a critical role in immune responses and the pathology of various diseases, including COVID-19. The manuscript delves into how changes in DNA methylation, histone modifications, and non-coding RNAs impact autophagy in the context of SARS-CoV-2 infection. The authors highlight that the virus can manipulate host cell autophagy through epigenetic mechanisms, thereby enhancing its replication and evading immune responses. For instance, SARS-CoV-2 can induce hypermethylation of autophagy-related genes, leading to their suppression and reduced autophagic activity, which facilitates viral persistence. Additionally, histone modifications such as acetylation and methylation play a significant role in regulating autophagy genes during infection, influencing the host's antiviral response. Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), are also critical in this regulation. The study identifies specific miRNAs that are dysregulated during COVID-19, which in turn modulate autophagy-related pathways. These miRNAs can either promote or inhibit autophagy, affecting viral replication and the severity of the disease. Furthermore, the article discusses potential therapeutic strategies targeting these epigenetic regulators to modulate autophagy in COVID-19 patients. By reversing the epigenetic changes induced by SARS-CoV-2, it may be possible to restore normal autophagic function, enhance antiviral responses, and improve clinical outcomes. In summary, this research provides insights into the complex interplay between epigenetic regulation and autophagy in COVID-19, highlighting new avenues for therapeutic intervention. The study underscores the potential of targeting epigenetic modifications to modulate autophagy and combat SARS-CoV-2 infection effectively.

Finally, Dalvand et al. investigates the intricate roles of Transforming Growth Factor Beta (TGFβ) and autophagy in the development of the cerebellum [15]. This research provides a comprehensive examination of how TGFβ influences autophagy and the consequent effects on early cerebellar development. TGFβ is a multifunctional cytokine that plays a pivotal role in regulating cellular processes such as growth, differentiation, and apoptosis. In the context of cerebellar development, TGFβ is essential for the formation and differentiation of neural structures. The study emphasizes that appropriate TGFβ signaling is crucial for neural progenitor cells to differentiate into specific neural cell types, which is fundamental for constructing the cerebellum's architecture. During early brain development, autophagy supports the survival and proper differentiation of neural cells. In summary, the article provides critical insights into how TGFβ regulates autophagy and impacts early cerebellar development. It highlights the necessity of proper TGFβ signaling for the modulation of autophagy, ensuring cellular homeostasis and neural differentiation during cerebellar formation. This research lays the groundwork for future studies aimed at understanding the interplay between TGFβ and autophagy in brain development and for developing potential therapeutic strategies for related neurological disorders.

The articles published in BB Reports special issue entitled "Regulation of Autophagy in cell fate and disease" collectively highlight the significant role of autophagy in various cellular processes and diseases. From hepatocyte protection in ischemia/reperfusion injury to the regulation of mechanical stress responses in pulmonary hypertension, and from cancer metabolism to nephroprotection against chemotherapy-induced damage, autophagy emerges as a pivotal mechanism influencing cell fate. Additionally, the modulation of autophagy in the context of COVID-19 and cerebellar development underscores its widespread impact across different biological systems. Autophagy serves as a critical cellular process for maintaining homeostasis by degrading and recycling damaged organelles and proteins. Its role in cell survival and adaptation to stress conditions is evident in multiple disease contexts. For instance, in cancer, autophagy supports tumor growth and survival under metabolic stress, while in ischemic liver cells, it mitigates cell death pathways. Conversely, dysregulated autophagy can contribute to disease progression, as seen in pulmonary hypertension and during viral infections like COVID-19. Autophagy's dual role as both a protector and a promoter of cell death highlights its complexity in regulating cell fate. In protective contexts, autophagy mitigates oxidative stress and apoptosis, as seen with desipramine's effects on hepatocytes and fenofibrate's protection against nephrotoxicity. However, in cancer, autophagy can support tumor survival, complicating therapeutic

approaches. Similarly, in pulmonary hypertension, autophagy may protect against mechanical stress but also contribute to maladaptive vascular remodeling.

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Dr. Saeid Ghavami, a leading scientisit on autophagy and cell death, is renowned for his pioneering research on autophagy's role in regulating cellular phenotype and developing therapeutic strategies in different diseases. With over 300 peer-reviewed publications, his work has significantly impacted understanding autophagy in disease models. Based at the University of Manitoba's Department of Human Anatomy and Cell Science, Dr. Ghavami's commitment to equity, diversity, and inclusion enriches his research environment, promoting a diverse and inclusive scientific community.

Dr. Shahla Shojaei is a prominent researcher in cell biology and autophagy, focusing on understanding the molecular mechanisms that regulate these processes in health and disease. Her research explores how autophagy influences cellular homeostasis, survival, and death, contributing to the development of novel therapeutic strategies for glioblastoma and neurodegenerative diseases. Dr. Shojaei's work has been instrumental in elucidating the complex interplay between autophagy and other cellular pathways, providing insights into the role of autophagy in cancer, neurodegeneration, and metabolic disorders. Her innovative approaches and significant contributions to the field have established her as a leading expert in cell biology and autophagy.

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