Exosomes and Acute Pancreatitis-Associated Acute Lung Injury

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Contributor: Qi Yang , Yalan Luo , Bowen Lan , Xuanchi Dong , Zhengjian Wang , Peng Ge , Guixin Zhang , Hailong Chen

Acute pancreatitis (AP) is a prevalent clinical condition of the digestive system, with a growing frequency each year. Approximately 20% of patients suffer from severe acute pancreatitis (SAP) with local consequences and multi-organ failure, putting a significant strain on patients' health insurance. According to reports, the lungs are particularly susceptible to SAP. Acute respiratory distress syndrome, a severe type of acute lung injury (ALI), is the primary cause of mortality among AP patients. Controlling the mortality associated with SAP requires an understanding of the etiology of AP-associated ALI, the discovery of biomarkers for the early detection of ALI, and the identification of potentially effective drug treatments. Exosomes are a class of extracellular vesicles with a diameter of 30–150 nm that are actively released into tissue fluids to mediate biological functions. Exosomes are laden with bioactive cargo, such as lipids, proteins, DNA, and RNA. During the initial stages of AP, acinar cell-derived exosomes suppress forkhead box protein O1 expression, resulting in M1 macrophage polarization. Similarly, macrophage-derived exosomes activate inflammatory pathways within endothelium or epithelial cells, promoting an inflammatory cascade response. On the other hand, a part of exosome cargo performs tissue repair and anti-inflammatory actions and inhibits the cytokine storm during AP.

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1. Introduction

Acute pancreatitis (AP) is a frequent occurring, acute abdominal illness. The majority of patients present with mild AP, which may spontaneously resolve. Nonetheless, approximately 20% of patients report severe AP (SAP) that is fast progressive and aggressive [1][2]. Acute lung injury (ALI) is a life-threatening condition characterized by diffuse interstitial and alveolar edema resulting from the damage of pulmonary microvascular endothelial cells (PMVECs) and alveolar epithelial cells (AECs) [3][4]. ALI and its severe form, acute respiratory distress syndrome (ARDS), are among the most prevalent consequences of SAP and are leading causes of mortality in SAP patients [5].

New insights into the pathogenesis of AP and associated ALI have emerged in recent years. The systemic inflammatory response (SIRS) caused by the abnormal activation of pancreatic enzymes, mitochondrial dysfunction, impaired autophagy, endoplasmic reticulum stress, programmed cell death, intestinal mucosal barrier damage, and bacterial translocation are the initiating factors of multiple organ dysfunction syndromes (MODS) in AP [6]. Key molecules causing pulmonary air–blood barrier disruption and alveolar edema include pancreatic, intestinal, and liver-derived non-coding RNAs (ncRNAs), damage-associated molecular patterns (DAMPs), and

pathogen-associated molecular patterns (PAMPs). Cross-signaling between immune cells (such as neutrophils, macrophages, and T cells) and parenchymal cells (such as acinar cells, intestinal epithelial cells, PMVECs, and AECs) is a crucial mechanism for maintaining the AP cytokine storm [7]. However, the molecular network of intercellular communication is intricate and requires immediate clarification. Exosome-related research has expanded quickly in recent years. The basics of exosomes, including the biogenesis, processes of secretion, and cargo they carry, have been steadily uncovered [8][9].

2. Exosomes and AP-Associated ALI

The molecular mechanisms involved in AP-associated ALI that lead to SIRS and diffuse alveolar damage have been studied in detail. Multiple signaling pathways are engaged during AP. To summarize, the activation of the cytokine storm is caused by the upregulation of extracellular mediators such as DAMPs, histones, and ncRNAs during AP. Intriguingly, emerging research has shown that the pancreas–lung axis [6] and the gut–lung axis [10] may mediate the cytokine storm in AP-associated ALI, and that exosomes may be major carriers of extracellular mediators transported along the signaling axis.

Zhu et al. discovered that plasma exosomal miR-216a was considerably elevated in AP patients with ALI compared to AP patients without ALI [11]. Exosomal miR-216a seems to be a particular modulator of inflammation in AP-induced ALI. As shown in animal investigations, miR-216a expression was undetectable in all organs save the pancreas, including the lung, gut, heart, and kidney. It is possible that exosomal miR-216a is pancreas-specific. Moreover, exosomal miR-216a enhanced the permeability of pulmonary microvascular endothelial cells, which was linked with the degree of ALI during AP. Xu et al. discovered that cold-inducible RNA-binding protein (CIRP) may play a crucial role in alveolar macrophage (AM) pyroptosis as well as neutrophil recruitment during AP-associated ALI [12]. The level of CIRP was found to be enhanced in the pancreatic tissue, serum, and lung tissue of AP rats by Xu and his colleagues. Interestingly, immunohistochemical staining revealed that pancreatic islet cells may be the predominant cell type that secretes CIRP, which may be an additional inflammatory mediator secreted by injured pancreatic tissue that induces ALI. In addition, Murao et al. discovered that CIRP may persist extracellularly as exosomes and mediate inflammation during sepsis.

The gut–lung axis is a commonly recognized pathophysiological signal of crosstalk between intestinal and pulmonary diseases. In the case of AP-associated ALI, intestinal damage and its subsequent response has an “amplifier” effect [13]. Firstly, intestinal barrier damage and increased intestinal permeability are prevalent in AP patients and models generated by a variety of causes [14][15]. Secondly, the intestinal barrier is a factor that exacerbates the inflammatory response to SIRS [16]. After intestinal barrier damage, the most direct consequence may be the “second strike” of intestine-derived endotoxins entering the circulation and lungs through the portal vein or mesenteric lymphatic system [17][18]. On the other hand, SIRS may be promoted by exosomes released from the injured gut during AP. Under physiological conditions, intestinal epithelial cells (IECs) or DC-derived exosomes carrying transforming growth factor-β, MHC class I and II complexes and co-stimulatory molecules coordinate the regulation of intestinal immunity and maintain immune homeostasis. However, miRNAs such as miR-122a and

miR-29a released from damaged IECs can exacerbate intestinal barrier damage and increase intestinal permeability [19].

3. The Therapeutic Potential of Exosomes in AP and Associated ALI

Aa a double-edged sword, exosomes release both anti-inflammatory and pro-inflammatory substances into the cells to which they bind. They regulate the inflammatory cascade response during AP by selectively binding downstream molecules and modulating receptor cell activity. As a result, researchers are considering exosomes as possible therapeutic targets. The first step in the chain of AP is pancreatic acinar cell damage. Recently, in vitro experiments confirmed that exosomes produced by acinar cells were shown to drastically lower intracellular ROS and the inflammatory factor level and ameliorate pathological pancreatic injury [20]. These findings show that injured cells may be able to heal tissue damage but that certain triggering elements are required. Several in vivo and in vitro studies demonstrated emodin's protective properties against AP-induced pancreatic injury, intestinal barrier dysfunction, and ALI [12][21]. Emodin was discovered to boost the differentiation and anti-inflammatory activity of regulatory T cells by stimulating the release of exosome-specific lncRNA taurine upregulated 1 (TUG1) from pancreatic acinar cells, hence limiting the development of AP [22]. Recent research suggests that the inflamed pancreas may release exosomes into the circulation during SAP. These exosomes have been shown to have a pro-inflammatory action. However, emodin may prevent "bad" exosomes from being secreting by acinar cells. Proteomics was employed to characterize the impact of rhodopsin on the plasma-derived exosome proteome in SAP rats. According to the results of the enrichment study, peroxisome proliferator-activated receptors (PPAR) signaling is the primary mechanism by which emodin influences the exosomal proteome. Mechanistic investigations showed that emodin protected the lungs by preventing exosome-mediated M1 polarization of alveolar macrophages via regulating PPAR signaling [23]. During AP-induced ALI, AECs are critical target cells in the lung, and their destruction directly leads to pulmonary edema and widespread alveolar injury. Evidence suggests that exosomes derived from AECs in ALI help to regulate the immune balance and the inflammatory cascade response [24]. As a natural antioxidant and anti-inflammatory agent, salidroside has been shown to protect against AP and ALI/ARDS caused by AP in mice. Activation of NF-κB, interleukin receptor-associated kinase, and tumor necrosis factor receptor-associated molecule 6 in AMs was inhibited by the salidroside-stimulated release of exosomal miR-146a from AECs and improved ALI in rats [25]. DAMPs and PAMPs activate AMs, an essential innate immune cell population during the outset of AP. They produce significant doses of inflammatory mediators that contribute to lung damage [26], unlike alveolar and alveolar epithelial cells. Similarly, pyroptotic AM-derived pyroptotic bodies increased AEC damage and vascular leakage [27]. Furthermore, the Hippo signaling pathway was activated in AECs by AMs-derived exosomal transfer RNA-derived fragments, which caused AECs ferroptosis and aided in the establishment of ALI [28]. Modulation of AMs-derived exosomes may therefore be a promising method for combating AP and associated ALI.

The therapeutic potential of mesenchymal stem cell (MSC)-derived exosomes cannot be overlooked in exosome-related treatment techniques [29][30][31]. Human umbilical cord mesenchymal stem cells (hucMSC) have been

frequently recognized for their capacity for self-renewal and multilineage differentiation, particularly for the bioactive chemicals they contain for tissue repair and the management of inflammation [32][33]. Han et al. discovered that hucMSC-derived exosomes showed a remarkable tissue regeneration potential in rats suffering from traumatic pancreatitis (trauma-induced non-infectious AP) [34]. In particular, hucMSC-Evs injected intravenously could colonize injured pancreatic tissue and inhibit inflammatory response and apoptosis of acinar cells, promoting damaged tissue repair [34]. A less frequent consequence of AP is myocardial injury, which is challenging to treat and has a high death rate [35]. MSC-derived exosomes were found to upregulate vascular hemophilia factor and vascular endothelial growth factor through the activation of the Akt/nuclear factor E2 related factors 2/heme oxygenase 1 signaling pathway, which led to the amelioration of SAP-induced myocardial injury [36]. Unfortunately, the previous research did not characterize the components transported by stem-cell-derived exosomes, i.e., the molecules that exert the protective effects. Xia et al., on the other hand, discovered that adipose-derived MSC-derived exosome increased AM mitochondrial function by transferring mitochondrial components to them, which led to a reduction in pulmonary inflammation in mice [37].

Researchers have discovered that edible plants may generate nanoscale EVs with shapes and components comparable to animal exosomes [38]. Furthermore, plant-derived exosomes are biocompatible and safe to consume, with no side effects or possible toxicity [39][40]. Plant-derived exosomes may penetrate biological barriers to transport lipid-soluble and hydrophilic target molecules to tissues in vivo, increasing the target molecules' bioavailability or effectiveness of the target molecules [41]. Ginger exosome-like nanoparticles (GELN) have been found to be taken up by lung macrophages and epithelial cells, with a preference for ACE2-positive cells. Furthermore, ginger GELN miRNA has the potential to bind to many locations in the SARS-CoV-2 virus genome and be transported to lung epithelial cells to decrease Nsp12 production and, consequently, lung inflammation [42]. As a result, plant-derived exosomes are potential AP therapeutic agents.

Exosomes maybe a therapeutic target for AP and related organ failures. Using novel medications to control the levels of lipids, proteins, and nucleic acids carried by exosomes, as well as the exosome-mediated drug delivery, offers fantastic potential to decrease the AP-induced cytokine storm. On the other hand, stem-cell-based exosome therapies have been in existence for some time and should be tested in AP clinical trials as soon as is feasible.

4. Exosome-Based Diagnostic Strategy

Compared with cell-free nucleic acids and proteins, exosome-specific nucleic acids and proteins are protected by a lipid bilayer and have better stability in the extracellular environment by avoiding degradation by RNA hydrolases [43][44]. In addition, exosomes are more accessible than solid biopsy samples and are present in almost all biological fluids, such as plasma, urine, saliva, ascites, breast milk, and amniotic fluid. Therefore, exosomes have been established as ideal biomarkers and have been widely used in disease diagnosis, prognosis evaluation, and treatment monitoring. The diagnostic and prognostic value of exosomes in pancreatic diseases such as pancreatic cancer and chronic pancreatitis has been widely confirmed [45][46][47][48].

Peripheral blood-derived exosomal miR-155, miR-216a, miR-21, (miR-603, miR-548ad-5p, miR-122-5p, miR-4477a, miR-192-5p, miR-215-5p, and miR-583), lncRNA PVT1, and MALAT1 [49] were linked with the severity of SAP and may provide new insight into the etiology of SAP and act as biomarkers of SAP. In addition, some AP serum/mesenteric lymph/plasma markers such as FBXL19-AS1 [50] and lnc-ITSN1-2 [51], miR-214-3p [52], miR-27a-5p [53], miR-217-5p [54], miR-193a-5p [55], miR-375 [56], miR-148a [57], miR-138-5p [58], miR-92b [59], miR-10a [59], miR-7 [60], miR-9 [60], miR-141 [61], miR-551b-5p [62], miR-126-5p [63], miR-24 [64], (miR-22-3p, miR-1260b, miR-762, miR-23b, miR-23a, miR-550a-5p, miR-324-5p, miR-484, miR-331-3p, miR-140-3p, and miR-342-3p [65]), miR-127 [66], miR-372 [67], miR-126-5p [68], miR-146 [69], miR-153 [70], miR-320-5p [55], Circ_0000284 [71], and Circ_0073748 [72], also exist in the exosome. These potential exosomal biomarkers also provide an important direction for the diagnosis and prognosis of AP in clinical applications.

Exosome-specific S100A8 correlates with the inflammatory response and predicts severity in individuals with SAP. Similarly, several free proteins and DNA are elevated in the plasma of patients with SAP, and this has implications for the diagnosis and prognostic assessment of the disease [73][74][75]. Moreover, the above substances such as HMGB1 [76], heat shock protein 70 [77], histones [49], CIRP [73], S100A12 [74], gamma-enolase [78], and mtDNA [75] have also been proven to be essential cargoes loaded by exosomes. Therefore, in the future, two areas of interest will be exploring whether the above exosome-specific cargoes can recognize AP and whether exosome-specific proteins or DNAs have better diagnostic performance than free proteins or DNAs.

In addition to blood samples, many exosomes exist in biological fluids, including urine and pancreatic juice. Urine samples are easy to obtain and non-invasive, which is desirable for both clinicians and patients. Several studies have found that nucleic acids and proteins carried by urine-derived exosomes have potential diagnostic value in pancreatic diseases [79][80][81]. In the case of AP, a 2014 study confirmed that urinary ketone bodies, glucose, plasma choline, and lipid levels were increased in patients' urine, while levels of urinary hippurate, creatine, and plasma-branched chain amino acids decreased. A biomarker panel of guanine, hippurate, and creatine reliably identified AP with high sensitivity and specificity [82]. Later, a proteomic study confirmed that the peak intensity ratio of urinary β-2 microglobulin to saponin B has a better diagnostic performance in patients with SAP, especially with renal injury and inflammation [83]. In short, urine is also a promising biospecimen for mining AP biomarkers. Exploring the changes in exosomal cargo in urine during AP is urgent.

Pancreatic juice is secreted by pancreatic acinar cells and duct wall cells, an alkaline liquid with a strong digestibility. In terms of accuracy and the characterization that best reflects the pathological mechanisms of AP, pancreatic fluid is second to pancreatic tissue and is a biofluid superior to blood and urine [84]. In 2018, Osteikoetxea et al. found that the detection and characterization of EVs in pancreatic juice are feasible and confirmed that mucin, CFTR, and MDR1 proteins carried by pancreatic juice-derived EVs are potential biomarkers of pancreatic cancer [85]. Later, Nakamura et al. found that miR-21 and miR-15 carried by pancreatic juice-derived exosomes have the potential to diagnose patients with PDAC and CP [86]. The diagnostic value of pancreatic juice examination in pancreas-related diseases is constantly updated. The changes in the exosomal cargo of pancreatic juice in AP patients should be explored as soon as possible.

Bronchoalveolar lavage fluid (BALF), which is in direct contact with lung tissue, is an ideal biologic fluid for the diagnosis of lung diseases [87]. Previous studies have found that exosomes derived from BALF have potential diagnostic value in patients with ALI/ARDS [88], chronic obstructive pulmonary disease [89], nodular pulmonary disease [90], lung cancer [91], lung infections [92], and asthma [93].

Because of their stability, exosome-specific ncRNAs and proteins have been employed as biomarkers in AP and associated ALI research. Exosome isolation from blood, pleural fluid, urine, ascitic fluid, alveolar lavage fluid, and pancreatic fluid is an emerging method of fluid biopsy with broad potential clinical applications, especially for patients with AP who are experiencing multi-organ failure. Exosome-specific ncRNA and protein detection are complicated by several variables, as has been described. Different clinical investigations on the expression of a specific exosomal cargo in the bodily fluids of AP patients may find contradictory results. To further establish the sensitivity and specificity of exosomal cargoes, substantial cohort studies are still required before their use can be advocated for in clinical applications.

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