Type 2 alveolar epithelial cell-derived circulating extracellular vesicle-encapsulated surfactant protein C as a mediator of cardiac infammation in COVID-19

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COMMENT

Type 2 alveolar epithelial cell-derived circulating extracellular vesicle-encapsulated surfactant protein C as a mediator of cardiac inflammation in COVID-19

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Abstract

Among the countless endeavours made at elucidating the pathogenesis of COVID-19, those aimed at the histopathological alterations of type 2 alveolar epithelial cells (AT2) are of outstanding relevance to the field of lung physiology, as they are the building blocks of the pulmonary alveoli. A merit of high regenerative and proliferative capacity, exocytotic activity resulting in the release of extracellular vesicles (EVs) is particularly high in AT2 cells, especially in those infected with SARS-CoV-2. These AT2 cell-derived EVs, containing the genetic material of the virus, might enter the bloodstream and make their way into the cardiovascular system, where they may infect cardiomyocytes and bring about a series of events leading to heart failure. As surfactant protein C, a marker of AT2 cell activity and a constituent of the lung surfactant complex, occurs abundantly inside the AT2-derived EVs released during the inflammatory stage of COVID-19, it could potentially be used as a biomarker for predicting impending heart failure in those patients with a history of cardiovascular disease.

Keywords Type 2 alveolar epithelial cell · Surfactant protein C · Extracellular vesicle · Cardiac inflammation · COVID-19

On the significance of surfactant proteins in COVID-19

The existence of an array of shared penta-peptides between the spike glycoprotein of 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2) and pulmonary surfactant-related proteins might explain the greater predilection of this newly identified strain, compared with that of other coronaviruses, for causing an insidiously obstinate pulmonary infection known better as 'coronavirus disease 2019' (COVID-19) [1]. The importance of this trans-species proteo-similarity, in terms of pathogen infectivity, is further emphasized once one considers the capacity of the lung surfactant complex for binding foreign material by means of its hydrophilic protein components [2], which could possibly be taken advantage of by structurally similar molecules, such as the SARS-CoV-2 spike protein, that would otherwise be targeted by the immune cells.

Consisting of hydrophobic lipid components as well, lung surfactant could also enhance the pathogenesis of COVID-19 by acting as a site for accumulation of SARS-CoV-2 particles [3], as the virus was recently reported to become lipid-soluble upon palmitoylation of its spike protein, which appears to be a prerequisite for successful entry of the virus into potential host cells [4].

The pressing nature of lung surfactant in the context of COVID-19 lies within the outstanding affinity of the SARS-CoV-2 spike protein for binding the ACE2 and TMPRSS2 proteins expressed on the surface of type 2 alveolar epithelial (AT2) cells [5], the functional compromise of which as a result of infection greatly impairs the production of lung surfactant. In fact, the issue regarding the COVID-19-related disintegration of lung surfactant was of sufficient significance to warrant a clinical trial on the efficacy of nebulised surfactant for the treatment of COVID-19 in patients requiring mechanical ventilation, due most often to 'acute respiratory distress syndrome' (ARDS) associated with surfactant depletion [6].

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While the hydrophobic constituents of the lung surfactant complex, including phosphatidylcholine, phosphatidylglycerol and cholesterol; make up as much as 90% of this biphasic fluid, and thus, are perhaps more extensively involved in SARS-CoV-2 infection, the less ample hydrophilic compartment of surfactant, consisting chiefly of surfactant proteins A to D [7], is the primary focus of the present diagnostic biomarker-oriented commentary.

Transmission of SARS-CoV-2 Infection from lungs to heart.

A life-threatening complication of COVID-19 [8] characterized by the flooding of alveoli with proteinaceous fluid [9], ARDS is a cytokine-induced condition that may adversely affect the integrity of lung surfactant [10] by instigating alveolar epithelial cell death [11], resulting in alveolar collapse and hypoxemia [8]. As a type of acute lung injury, ARDS was recently suggested to be associated with increased levels of murine intra-alveolar 'microvesicles' (MVs) [12]; a common type of 'extracellular vesicles' (EVs) spanning 100–1000 nm in size. While they are generally thought to be the product of macrophage activity, particularly in response to infectious agents such as viruses, EVs released in the alveoli can also be the progeny of type 2 alveolar epithelial cells (AT2) [9], since they are the first line of defence upon exposure to inhaled stimuli. This was recently confirmed by analyzing the content of 'broncho-alveolar lavage fluid' (BALF), from which a large amount of EVs were extracted in mice whose lower respiratory tract had been subject to hyperoxia. These AT2-derived 50–120 nm EVs, released in response to 'endoplasmic reticulum' (ER) stress, are thought to trigger the activity of alveolar macrophages by inducing a pro-inflammatory signaling pathway. However, the pro-inflammatory effect of AT2-derived EVs is not merely restricted to the lung, as they might enter the circulation and elicit immune response in a systemic fashion [11].

Based on the present notion, these 'COVID-19-associated AT2-derived circulating EVs' (CAT2 cEVs) could be used for evaluating the clinical outcome of COVID-19, particularly in patients with underlying or suspected cardiovascular disease. That is because SARS-CoV-2 RNA-containing extracellular vesicles isolated from A549 cells–a type of human basal epithelial cell–are highly likely to target 'human pluripotent stem cell-derived cardiomyocytes' (hiPSC-CMs), bringing about the infection of cardiac tissue with SARS-CoV-2. Table 1 lists a number of physiological/pathological conditions in which cardiomyocytes are the recipient or target cells for cEVs released by different cell lines.

As cardiomyocytes are not directly targeted by SARS-CoV-2, in spite of expressing ACE2 [13], the recent findings regarding the affinity of SARS-CoV-2^{+} AT2-derived cEVs for cardiomyocytes might provide us with an explanation for the lesser-studied inter-organic transmission of infection in COVID-19, and could even help us clinically predict the occurrence of an impending cardiovascular complication, e.g., myocarditis and heart failure, as a consequence of COVID-19.

Myocarditis and heart failure in COVID-19

While histopathological findings suggestive of myocarditis are only observed in less than 2% of COVID-19 patients [14], when present, myocarditis may put individuals with SARS-CoV-2 infection at a mortality risk of about 15%, which is roughly 5 times higher than the overall mortality rate of 0.8–3% reported for otherwise healthy COVID-19 patients. This mortality rate of 15% might go as high as 27.3% in the case of Takotsubo cardiomyopathy, which is the actual myocardial pathology in 48% of cases suspected to have SARS-CoV-2-related myocarditis [15]. The recent identification of SARS-CoV-2 RNA in the myocardial tissue of deceased COVID-19 patients [16] strongly suggests that the myocardial injury reported in about 7% of patients hospitalized due to COVID-19 [17] might actually be the result of viral infection, rather than collateral immune-based damage.

Regardless of the clinical nature of COVID-19, and even its detectability, markers of SARS-CoV-2 infection can still be isolated from the myocardial tissue of individuals with potential past exposure to the virus, as indicated by an investigation noting the presence of SARS-CoV-2 nucleoprotein in the pulmonary vein wall of donors with negative COVID-19 test results [18]. The involvement of pulmonary veins highlights the role of these major vessels as pathways for transmission of disease-inducing material from the lungs to the heart, which is not an unprecedented assumption in the case of cEVs, as one study reported higher concentrations of tumor-derived cEVs in the pulmonary venous blood of deceased patients with non-small cell lung cancer (NSCLC), compared with that of their peripheral venous blood [19].

Similar to tumor-derived cEVs isolated from the pulmonary venous blood, draining the lungs to the heart, CAT2 cEVs might take the same route to transfer disease-inducing material from their parent type 2 alveolar epithelial cells to cardiomyocytes, a hypothesis illustrated in Fig. 1.

Table 1 An overview of investigations on the interactions between sEVs and cardiomyocytes, as recipient cells, in different pathological/physiological conditions

Condition	EV Source	EV recipient	EV size (nm)	EV content	Process affected	Citation
MIRI	PBCs	CMs	100–200	↓ miR-17-3p	↑ Necrosis	[31]
Sepsis	Macrophages	CMs	50–200	↑ miR-24-3p	↓ Apoptosis	[32]
HF	RBCs	CMs	50–200	↑ miR-451	↑ Proliferation	[33]
AMI	cEVs	CMs	50–300	↓ miR-342-3p	↑ Apoptosis	[34]
Obesity	Adipocytes	CMs	30–500	↑ Mitochondrial particles	↑ Oxidative stress	[35]
Uremia	ECs	CMs	50–150	↑ lncRNA-ANRIL	↑ Autophagy	[36]
Thalassemia	RBCs	CMs	100–400	↑ Ferritin	↑ Proliferation	[37]
CABG	cEVs	CMs	Unspecified	↑ GPX3	↓ Apoptosis	[38]
HF	CMs	CMs	100–300	↑ miR-30d	↓ Apoptosis	[39]
HF	CFs	CMs	50–300	↑ miR-27a	↑ Hypertrophy	[40]
Diabetes	Adipocytes	CMs	< 300	↑ miR-130b-3p	↑ Apoptosis	[41]
MI	Macrophages	CMs	50–150	↑ IL-1α ↑ IL-1β	↑ Pyroptosis	[42]
Exercise	cEVs	CMs	30–100	↑ miR-342-5p	↓ Apoptosis	[43]
Obesity	cEVs	CMs	Unspecified	↑ miR-29a	↓ Mitochondrial activity	[44]
Diabetes	cEVs	CMs	Unspecified	↑ Rab-1A	↑ Apoptosis	[45]
Obesity	cEVs	CMs	Unspecified	↑ miR-122	↓ Mitochondrial activity	[46]
Obesity	cEVs	CMs	Unspecified	↑ miR-194	↓ Mitochondrial activity	[47]
MI	cEVs	CMs	Unspecified	↓ miR-21	↑ Apoptosis	[48]
Stroke	ECs	CMs	Unspecified	↓ miR-126	↑ Hypertrophy	[49]
PPCM	ECs	CMs	50–800	↑ miR-146a	↑ Apoptosis	[50]
Health	cEVs	CMs	< 100	↑ HSP-70	↓ Apoptosis	[51]

MIRI myocardial ischemia/reperfusion injury, *PBCs* peripheral blood cells, *CMs* cardiomyocytes, *HF*, heart failure, *RBCs* red blood cells, *AMI* acute myocardial injury, *cEVs* circulating extracellular vesicles, *ECs* endothelial cells, *CABG* coronary artery bypass graft, *GPX3*, glutathione peroxidase 3, *CFs* cardiac fibroblasts, *MI* myocardial infarction, *PPCM* peripartum cardiomyopathy

Circulating extracellular vesicles in COVID-19

As of recent, an investigation on COVID-19 patients demonstrated increased levels of large and small cEVs. While the former, with a size ranging from 100 to 400 nm, were mostly upregulated in patients with moderate COVID-19, small cEVs 30–100 nm in size were shown to occur more frequently in the serum of patients with severe disease. These small cEVs contained higher levels of caspase 3 and interleukin-6 receptor (IL6R) in patients with severe disease [20], which is consistent with their pro-inflammatory effects.

While the exact origin of these cEVs were not indicated by the study in question, another investigation published shortly after reported elevated concentrations of cleaved caspase 3 and IL-6, along with the AT2 cell marker 'surfactant protein C' (SP-C), in COVID-19-associated cEVs originating from alveolar epithelial cells, among other cell types. Based on this particular study, the content of CAT2 cEVs depended substantially on the chronological stage of COVID-19, as patients in the second phase or hyperinflammatory stage of the disease tended to have higher concentrations of these three markers in their blood [21]. This could indicate a potential correlation among SARS-CoV-2-induced inflammation, the content of CAT2 cEVs and COVID-19-associated myocardial injury, since the incidence of acute cardiac injury is approximately 3 times higher in critically ill COVID-19 patients admitted to the intensive care unit [17].

The EV-encapsulated caspase 3 is thought to be responsible for alveolar macrophage activation by inducing a Rho-associated kinase known as 'coiled-coil-containing protein kinase 1' OR ROCK1 [11], which is mostly involved in cell adhesion and motility, apoptosis and remodelling of the extracellular matrix, with potential stimulatory effects on pathological processes leading to cardiovascular disease, e.g., heart failure. Once activated, ROCK1 is capable of triggering the activity of caspase 3, resulting in a positive feed-forward regulatory loop observed in murine cardiomyocytes undergoing pressure overload-related hypertrophy [22].

In this sense, the ROCK1 signaling pathway could be implicated in SARS-CoV-2 infection as well, since around 20% of COVID-19 patients who require hospitalization are estimated to develop acute heart failure [23]. As there is not a distinguishable difference in the 'left ventricular end diastolic' and 'left ventricular end systolic' volume indices

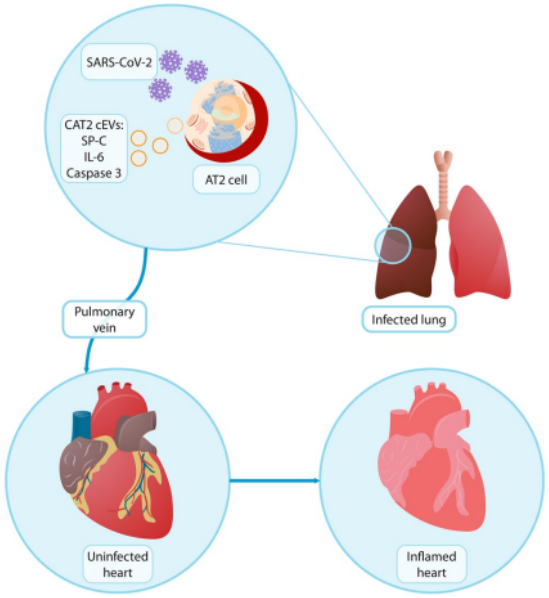

Fig. 1 A simplified diagram illustrating a proposed pathway for infection of cardiomyocytes with SARS-CoV-2 by means of COVID-19-associated type 2 alveolar epithelial cell-derived circulating extracellular vesicles through the pulmonary vein as a major route from the lungs to the heart. Once the alveolar epithelial cells lining the inner surface of pulmonary alveoli are infected with SARS-CoV-2, they release a substantial amount of extracellular vesicles containing SP-C, IL-6 and cleaved caspase 3. These AT2-derived EVs are then drained via small veins that ultimately join together to form the pulmonary veins, draining into the left atrium of the heart. Once inside the cardiac chamber, the three pro-inflammatory molecules, particularly SP-C, might induce cardiac inflammation or myocarditis, ultimately resulting in heart failure

(LVEDVI/LVESVI) between the surviving and non-surviving COVID-19 patients, and the right ventricular fractional area change (RV-FAC) is considerably lower in non-survivors [24], it is possible that the acute heart failure reported in COVID-19 patients might be a consequence of pressure overload, rather than volume overload; a speculation consistent with the presumed function of CAT2 cEV-encapsulated caspase 3 in COVID-19.

Surfactant protein C; a potential biomarker for impending heart failure in COVID-19.

A typical marker of AT2 cell activity, SP-C was shown to alleviate 'acute lung injury' (ALI) when administrated by means of 'mesenchymal stem cell' (MSC)-derived exosomes to AT2 cells undergoing phosgene-induced damage [25], providing evidence that the integrity of pulmonary alveoli is correlated with the intra-alveolar content of SP-C.

Covering only 7% of the alveolar surface [8], AT2 cells are the only type of alveolar epithelial cells that express ACE2 and TMPRSS2, two important receptors for SARS-CoV-2, as fully differentiated AT1 cells often lack these two receptors [26]. In this sense, while it would appear that only a very limited proportion of the alveolar surface is susceptible to SARS-CoV-2 infection, one should not overlook the regenerative capacity of AT2 cells, as their type I counterparts are expendable.

It is thought that disintegration of the alveolar-capillary barrier as a result of SARS-CoV-2 infection might lead to hypoxia, and ultimately, ventilation-perfusion mismatch [27]. This could trigger the expression of ACE2 and TMPRSS2 in AT2 cells, accelerating viral entry and the rate of infection with SARS-CoV-2. As AT2 cells are capable of proliferation, they begin to repopulate the alveolar surface with new $ACE2^{+}/TMPRSS2^{+}$ cells, bringing about a vicious cycle that eventually causes respiratory failure in cases with COVID-19-related ARDS [8].

From a histopathological point of view at the level of the alveolar-capillary barrier, severe COVID-19 is characterized by clusters of progenitor AT2 cells incapable of fully transitioning into their AT1 counterparts, indicating an in-effect regeneration program initiated by AT2 cells in response to COVID-19-related alveolar damage. Nonetheless, this regeneration program cannot be completed due to the inflammation-associated 'pre-AT1 transitional cell state' (PATS), giving rise to an ineffectively differentiated population of AT2 cells known as 'damage-associated transient progenitors' (DATPs), which exhibit downregulated expression of SP-C, while displaying increased transcription of genes such as 'hypoxia-inducible factor 1-alpha' (HIF-1α) [28]. A mediator of cell proliferation expressed in response to hypoxia, among others, HIF-1α is upregulated in the blood of COVID-19 patients, enhancing SARS-CoV-2 infection [29].

The enrichment of HIF-1α signaling pathway in DATPs [28] could be responsible, in part, for the increased level of CAT2 cEV-encapsulated SP-C, since hypoxia may actually induce the expression of SP-C in alveolar epithelial cells to some extent [10]. On the contrary, however, there is also solid evidence suggesting downregulation of SP-C in $SARS\text{-}CoV\text{-}2^{+}$ AT2 cells [26]. While this might contradict the very concept of the present commentary, it should be noted that not all AT2 cells in the lower respiratory tract of COVID-19 patients turn into DATPs. There are regions of AT2 cell hyperplasia in the lungs of COVID-19 patients that intersperse clusters of surfactant protein C-lacking AT2 cells [30] (presumably DATPs). These hyperplastic AT2 cells, rich in SP-C, could very well be the source of CAT2 cEVs in patients with SARS-CoV-2 infection. Still, the veracity of this speculation needs to be confirmed by further investigations.

Conclusion

Extracellular vesicles have been a particular area of interest for clinical and laboratory research in respiratory medicine, owing to the high exocytotic activity of AT2 cells, among other cell types in the respiratory epithelium. Alveolar epithelial cell-derived EVs might serve local functions at the level of the alveoli, or enter the bloodstream and assume wide-scale roles in the form of cEVs, which can be utilized clinically as biomarkers for important respiratory diseases, e.g., NSCLC, and even COVID-19; a rather lesser-known malady of the lower respiratory tract. Considering the receptiveness of cardiomyocytes to A549 cell-derived SARS-CoV-2 RNA-containing EVs, the clinically significant incidence of heart failure in critically ill COVID-19 patients, the higher concentration of alveolar epithelial cell-derived EVs in the pulmonary vein, and the substantial SP-C content of CAT2 cEVs, the present commentary suggests surfactant protein C as a circulating biomarker for predicting impending heart failure in COVID-19 patients with cardiovascular risk factors.

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Declarations

Conflict of interest No conflicts of interest, financial or otherwise, are declared by the authors.

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