Endothelial Extracellular Vesicles

Subjects: Biology

Contributor: Allison Mathiesen

Extracellular vesicles (EVs) produced by the endothelial cells mirror the remarkable molecular heterogeneity of their parent cells. Cargo molecules carried by EVs were shown to contribute to the physiological functions of endothelium and may support the plasticity and adaptation of endothelial cells in a paracrine manner. Endothelium-derived vesicles can also contribute to the pathogenesis of cardiovascular disease or can serve as prognostic or diagnostic biomarkers. Finally, endothelium-derived EVs can be used as therapeutic tools to target endothelium for drug delivery or target stromal cells via the endothelial cells.

Keywords: exosomes ; microvesicles ; heterogeneity ; dysfunction ; cardiovascular disease ; COVID-19

1. Introduction

Endothelium is a key gateway for communication between blood and stroma. Recent evidence highlights the remarkable heterogeneity and plasticity of the endothelial cells in development, health and disease. The molecular signatures of the stromal cells in different organs are reflected within the transcriptome of their resident vascular endothelia. Endothelial functional and molecular zonation within various tissues shows how endothelial heterogeneity serves to optimize physiologic tissue function. In disease, endothelium can undergo dedifferentiation or transdifferentiation, thereby contributing to vascular maladaptation and dysfunction. The rich vesicular network of the endothelial cells designed to facilitate the regulated transport of hormones, growth factors, nutrients and pathogens also contributes to the biogenesis and uptake of extracellular vesicles (EVs). Due to its unique position as the interface between blood and lymph, the endothelium is a significant contributor to the circulating secretome. The particulate secretomes of endothelia mirror their molecular heterogeneity and may support plasticity and adaptation of endothelial cells within or between different vascular beds while also having significant functional impacts on circulating cells, including immune cells in blood or lymph. Therefore, EVs can support the physiological adaptation of endothelium or can contribute to the pathogenesis of vascular diseases and other diseases.

2. The Biological and Clinical Relevance of Endothelial EVs in COVID-19

COVID-19 infection caused by the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was shown to be associated with endothelial dysfunction manifested as increased formation of micro-thrombi, cytokine production by endothelium and deregulated immune responses [1]. Endothelial cells reportedly express both ACE2 and TMPRSS2 which makes them susceptible to direct viral entry and infection. However, both infected and uninfected endothelial cells may manifest dysfunction, which suggests that direct viral infection is not the solely responsible mechanism. EVs share some structural similarities with viruses, and recently it was found that viruses can exploit EVs for cellular exit or viral protein transfer, and EVs exploit viral entry mechanisms for cargo delivery [2][3]. Endothelium contributes significantly to the circulating EVs in blood and lymph, and it is conceivable to propose that endothelium-derived EVs could be responsible for the dissemination of pro-coagulant and pro-inflammatory molecules that can perpetuate the dysfunction initiated in infected cells. Indeed, proteomic analysis of the EV in plasma of patients with different degrees of COVID-19 severity showed distinct protein signatures that correlate with clinical manifestations of the disease [4]. In a separate study, Barberis et al. found that the proteome of the circulating EVs contained a large number of immune, pro-inflammatory and pro-coagulant proteins, and identified SARS-Cov-2 RNA in the exosomal cargo [5]. In a recent study, human lung endothelial cells exposed to the plasma of patients with severe disease and the plasma of patients with mild disease showed a significant difference in caspase3/7 and decreased cell survival in the former [6]. In the same study, authors showed that compared to asymptomatic controls, EVs isolated from patients on oxygen support with severe disease displayed increased protein expression for pro-thrombotic/endothelial injury factors such as t-PA, TF and vWF, along with proinflammatory proteins of the TNFα and IL 6 families. In another study, Rosell et al. showed that severe SARS-CoV-2 infection induces the release in circulation of EVs that harbor tissue factor and are likely to contribute to thrombosis in infected patients [7]. The presence of functional tissue factor in EVs showed correlation between its pro-coagulant activity

and disease severity and was positively associated with mortality. Interestingly, in both studies, pro-thrombotic signatures were found in large circulating EVs and it was proposed, albeit without providing direct evidence, that they are primarily endothelium derived.

The data obtained so far strongly suggest the role of endothelium and endothelium-derived EVs in the pro-thrombotic and pro-inflammatory effects of SARS-CoV-2 infection in patients with COVID-19. Several studies showed that the protein profile of the circulating EV cargo is associated with disease severity and even mortality in COVID-19 patients. This makes EVs promising clinical biomarkers for disease prognosis and potentially for the response to future therapeutic approaches to mitigate the severe respiratory manifestation of the disease.

3. Concluding Remarks

The extraordinary molecular and functional diversity of the vascular endothelium supports the notion that endothelial cells are programmed to serve specific functional adaptations of the vascular bed where they belong, which, in turn, is fine-tuned to the physiologic requirements of the adjacent stroma. We emphasized the physiological heterogeneity of endothelial cells along with their maladaptive plasticity in disease. Uniquely positioned at the interface between the fluid conduits and tissue parenchyma, endothelial cells control the bi-directional traffic of macromolecules, cells and EVs between the two compartments. Endothelium is therefore both a major contributor to circulating EVs and a gatekeeper of vesicular traffic between stroma and blood. Moreover, the EVs' cargos and rates of biogenesis by the endothelium reflect the molecular and functional phenotypes of the endothelial cells of origin. In fact, EVs can disseminate molecules that originate in their parent cells to distant endothelial or non-endothelial cells and can alter their phenotypes. Recent findings support the roles of endothelial vesicles in health and disease, and highlighted the gaps in knowledge and the limitations of current experimental approaches and research paradigms. Finally, endothelial EVs have the potential as prognostic or diagnostic biomarkers and evaluated their promise as therapeutic targets or as tools for targeted delivery of other therapeutics. The recent advances in single cell biology made all of us re-evaluate the biological paradigms surrounding cellular identity and plasticity and much-needed approaches are emerging for studying the biology of single EVs. After all, personalized medicine for cardiovascular disease should not only be the prerogative for holistic treatment of individuals, but also for personalized healing of one endothelial cell and one EV at a time, which collectively should benefit the healing of the cardiovascular system.

References

1. Oxford, A.E.; Halla, F.; Robertson, E.B.; Morrison, B.E. Endothelial cell contributions to COVID-19. Pathogens 2020, 9, 785.
2. Yoshikawa, F.S.Y.; Teixeira, F.M.E.; Sato, M.N.; Oliveira, L.M.d.S. Delivery of microRNAs by extracellular vesicles in viral infections: Could the news be packaged? Cells 2019, 8, 611.
3. Dogrammatzis, C.; Waisner, H.; Kalamvoki, M. Cloaked viruses and viral factors in cutting edge exosome-based therapies. Front. Cell Dev. Biol. 2020, 8, 376.
4. Pocsfalvi, G.; Mammadova, R.; Ramos Juarez, A.P.; Bokka, R.; Trepiccione, F.; Capasso, G. COVID-19 and extracellular vesicles: An intriguing interplay. Kidney Blood Press. Res. 2020, 45, 661–670.
5. Barberis, E.; Vanella, V.V.; Falasca, M.; Caneapero, V.; Cappellano, G.; Raineri, D.; Ghirimoldi, M.; De Giorgis, V.; Puricelli, C.; Vaschetto, R.; et al. Circulating exosomes are strongly involved in SARS-CoV-2 Infection. Front. Mol. Biosci. 2021, 8.
6. Krishnamachary, B.; Cook, C.; Spikes, L.; Chalise, P.; Dhillon, N.K. The potential role of extracellular vesicles in COVID-19 associated endothelial injury and pro-inflammation. medRxiv 2020.
7. Rosell, A.; Havervall, S.; von Meijenfeldt, F.; Hisada, Y.; Aguilera, K.; Grover, S.P.; Lisman, T.; Mackman, N.; Thålin, C. Patients with COVID-19 have elevated levels of circulating extracellular vesicle tissue factor activity that is associated with severity and mortality—Brief report. Arterioscler. Thromb. Vasc. Biol. 2021, 41, 878–882.

Retrieved from https://encyclopedia.pub/entry/history/show/22299