Extracellular Vesicles

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Tobacco smoking is prevalent among people living with HIV (PLWH). It is known to increase viral replication and exacerbate HIV associated conditions. Some reports demonstrate a conflicting impact of cigarette smoke on PLWHA in terms of neurocognitive disorders, which further strengthens the necessity to study whether cigarette smoking is a causative factor for HAND in PLWHA. One possible mechanistic pathway of tobacco smoking-induced HIV pathogenesis and HAND could be the transportation of oxidative stress-related agents and inflammatory modulators via extracellular vesicles (EVs). EV are nanosized vesicles, that are formed and released from most of the mammalian cells and these are considered as cellular messengers because of their capability to transport the functional messages from cells to other distant cells. This review focuses on recent advances in the field of EVs with an emphasis on smoking-mediated HIV pathogenesis and HIV-associated neuropathogenesis.

Keywords: HIV ; Tobacco smoking ; Extracellular vesicles ; Inflammation ; Oxidative stress

1. Introduction

Once a lethal pandemic, HIV has now taken the form of a chronic condition. As of 2018, at least 37.9 million people were living with HIV, with more than a million new cases each year [1]. The majority of these people living with HIV/AIDS (PLWHA) have a life expectancy comparable to healthy adults, which is attributed to remarkable advances in medicine, especially the introduction of combination anti-retroviral therapy (cART) [2][3][4][5]. However, a huge portion of PLWHA have a poor quality of life and suffer from high morbidity and mortality associated with drugs of abuse, including tobacco. More than 40% of PLWHA in the USA are cigarette smokers, which severely affect their life expectancy, reducing the average life span by over 6 years [6][7][8]. Mortality due to non-AIDS related malignancies is almost two-fold higher in HIV-positive smokers, irrespective of the use of cART [9]. Non-adherence to cART and/or attenuated treatment efficacy in HIV-positive smokers could possibly increase the risk of morbidity and mortality [10][11]. Smoking cessation can improve life expectancy, although studies have shown that smoking cessation is hard to achieve [12]. While the exact mechanistic pathway for smoking-mediated exacerbation of HIV pathogenesis is not fully understood, our studies have shown that tobacco smoke aggravates HIV pathogenesis, in part via the induction of cytochrome P450 (CYP)-mediated metabolism and activation of cigarette smoke constituents, resulting in oxidative stress [13][14][15][16][17][18]. In particular, we have demonstrated that benzo(a)pyrene (B(a)p), a potent component of cigarette smoke, exacerbates HIV replication via CYP-induced oxidative stress followed by the NF-κβ pathway [13].

Approximately 50% of PLWHA demonstrate a pattern of cognitive, motor, and behavioral dysfunction, cumulatively termed HIV-associated neurocognitive disorders (HAND) [19][20][21]. In the presence of cigarette smoke, the risk of peripheral neuropathy and HAND in PLWHA increases significantly [7][22][23][24][25]. Some reports demonstrate a conflicting impact of cigarette smoke on PLWHA in terms of neurocognitive disorders [26][27][28], which further strengthens the necessity to study whether cigarette smoking is a causative factor for HAND in PLWHA.

One possible mechanistic pathway of tobacco smoking-induced HIV pathogenesis and HAND could be the transportation of oxidative stress-related agents and inflammatory modulators via extracellular vesicles (EVs), commonly referred to as exosomes prior to 2018. EVs are biological nanoparticles and are released by almost all cells [29][30]. They are considered as both inter and intra-cellular messengers, able to modify their cargo according to the condition or stimulus affecting the parent cells [31][32], which upon internalization by recipient cells, can modulate the pathophysiological state in those cells [33][34]. EVs play an important role in HIV pathogenesis - either in improving or deteriorating the existing condition; however, the exact role of EVs in HIV pathogenesis is poorly understood [35][36]. Currently, only a handful of studies have investigated the role of EVs in smoking-mediated toxicity in the setting of HIV [37][38][39].

2. Discussion

The complete eradication of HIV is not currently feasible, with a few exceptions [40][41], due to viral latency in cellular reservoirs, e.g. CD4 T cells, cells of the myeloid lineage (monocytes and macrophages) and dendritic cells [42][43][44][45]. Monocytes and macrophages are considered one of the most suitable cells for studying viral latency due to their long lifespan, as well as their ubiquitous presence throughout the body, including the brain [43][45][46]. EVs derived from monocytes and macrophages potentially have a profound effect on recipient cells [47][48]. For example, we have previously reported that EVs derived from uninfected monocytes protect recipient cells due to the specific packaging of protective elements [39], manuscript under revision). Conversely, HIV-infected macrophage-derived EVs lose this defense capacity, as evidenced by a higher viral load and increased cellular toxicity [39]. Proteomic and cytokine analyses of plasma EVs obtained from HIV-positive and negative smokers demonstrated a differential packaging of proteins in the EVs [37][49]. In addition, macrophage-derived EVs can readily cross the blood brain barrier, suggesting the potential role of EVs in either disseminating or alleviating HIV and HAND pathogenesis [30].

Evidently, there is a strong correlation between cigarette smoking and HIV and/or HAND pathogenesis as demonstrated via EVs. Nevertheless, there are unresolved questions to be answered. For example, what is the true nature/role of EVs in smoking-mediated HIV and HAND pathogenesis? Can we inhibit the viral transfection and oxidative stress through EVs? Is there any therapeutic application of EVs in this context? Can the components of EVs be used as biomarkers for HIV-tobacco smoking interactions that lead to HAND? Very recently, especially in the last five years, more and more studies are being conducted to answer these questions. This niche field has drawn researchers to connect the dots between HIV, cigarette smoking, HAND and EVs, and whether oxidative stress acts as a driving force to exacerbate the conditions.

References

1. HIV.Gov. The Global HIV/AIDS Epidemic. Available online: https://www.hiv.gov/hiv-basics/overview/data-and-trends/global-statistics (accessed on 31 March 2020).
2. Teeraananchai, S.; Kerr, S.J.; Amin, J.; Ruxrungtham, K.; Law, M.G. Life expectancy of HIV-positive people after starting combination antiretroviral therapy: A meta-analysis. Hiv Med. 2017, 18, 256–266. [Google Scholar] [CrossRef] [PubMed]
3. Samji, H.; Cescon, A.; Hogg, R.S.; Modur, S.P.; Althoff, K.N.; Buchacz, K.; Burchell, A.N.; Cohen, M.; Gebo, K.A.; Gill, M.J.; et al. Closing the gap: Increases in life expectancy among treated HIV-positive individuals in the United States and Canada. PLoS ONE 2013, 8, e81355. [Google Scholar] [CrossRef] [PubMed]
4. Ray, M.; Logan, R.; Sterne, J.A.; Hernandez-Diaz, S.; Robins, J.M.; Sabin, C.; Bansi, L.; van Sighem, A.; de Wolf, F.; Costagliola, D.; et al. The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals. Aids 2010, 24, 123–137. [Google Scholar] [CrossRef] [PubMed]
5. Romley, J.A.; Juday, T.; Solomon, M.D.; Seekins, D.; Brookmeyer, R.; Goldman, D.P. Early HIV treatment led to life expectancy gains valued at $80 billion for people infected in 1996-2009. Health Aff. 2014, 33, 370–377. [Google Scholar] [CrossRef]
6. Reddy, K.P.; Parker, R.A.; Losina, E.; Baggett, T.P.; Paltiel, A.D.; Rigotti, N.A.; Weinstein, M.C.; Freedberg, K.A.; Walensky, R.P. Impact of Cigarette Smoking and Smoking Cessation on Life Expectancy Among People With HIV: A US-Based Modeling Study. J. Infect. Dis. 2016, 214, 1672–1681. [Google Scholar] [CrossRef]
7. Reynolds, N.R. Cigarette smoking and HIV: More evidence for action. Aids Educ. Prev. Off. Publ. Int. Soc. Aids Educ. 2009, 21, 106–121. [Google Scholar] [CrossRef]
8. Helleberg, M.; Afzal, S.; Kronborg, G.; Larsen, C.S.; Pedersen, G.; Pedersen, C.; Gerstoft, J.; Nordestgaard, B.G.; Obel, N. Mortality attributable to smoking among HIV-1-infected individuals: A nationwide, population-based cohort study. Clin. Infect. Dis. Off. Publ. Infect. Dis. Soc. Am. 2013, 56, 727–734. [Google Scholar] [CrossRef]
9. Helleberg, M.; May, M.T.; Ingle, S.M.; Dabis, F.; Reiss, P.; Fatkenheuer, G.; Costagliola, D.; d'Arminio, A.; Cavassini, M.; Smith, C.; et al. Smoking and life expectancy among HIV-infected individuals on antiretroviral therapy in Europe and North America. Aids 2015, 29, 221–229. [Google Scholar] [CrossRef]
10. Shuter, J.; Bernstein, S.L. Cigarette smoking is an independent predictor of nonadherence in HIV-infected individuals receiving highly active antiretroviral therapy. Nicotine Tob. Res. Off. J. Soc. Res. Nicotine Tob. 2008, 10, 731–736. [Google Scholar] [CrossRef]
11. Kariuki, W.; Manuel, J.I.; Kariuki, N.; Tuchman, E.; O'Neal, J.; Lalanne, G.A. HIV and smoking: Associated risks and prevention strategies. Hiv Aids 2016, 8, 17–36. [Google Scholar] [CrossRef]

12. Brath, H.; Grabovac, I.; Schalk, H.; Degen, O.; Dorner, T.E. Prevalence and Correlates of Smoking and Readiness to Quit Smoking in People Living with HIV in Austria and Germany. PLoS ONE 2016, 11, e0150553. [Google Scholar] [CrossRef] [PubMed]
13. Ranjit, S.; Sinha, N.; Kodidela, S.; Kumar, S. Benzo(a)pyrene in Cigarette Smoke Enhances HIV-1 Replication through NF-kappaB Activation via CYP-Mediated Oxidative Stress Pathway. Sci. Rep. 2018, 8, 10394. [Google Scholar] [CrossRef] [PubMed]
14. Rao, P.; Ande, A.; Sinha, N.; Kumar, A.; Kumar, S. Effects of Cigarette Smoke Condensate on Oxidative Stress, Apoptotic Cell Death, and HIV Replication in Human Monocytic Cells. PLoS ONE 2016, 11, e0155791. [Google Scholar] [CrossRef] [PubMed]
15. Kumar, S.; Rao, P.; Sinha, N.; Midde, N.M. Cytochrome P450 and Oxidative Stress as Possible Pathways for Alcohol- and Tobacco-Mediated HIV Pathogenesis and NeuroAIDS. In Neuropathology of Drug Addictions and Substance Misuse; V.R., P., Ed.; 2016; Volume 1, pp. 179–188. [Google Scholar]
16. Ranjit, S.; Midde, N.M.; Sinha, N.; Patters, B.J.; Rahman, M.A.; Cory, T.J.; Rao, P.S.; Kumar, S. Effect of Polyaryl Hydrocarbons on Cytotoxicity in Monocytic Cells: Potential Role of Cytochromes P450 and Oxidative Stress Pathways. PLoS ONE 2016, 11, e0163827. [Google Scholar] [CrossRef]
17. Ande, A.; McArthur, C.; Ayuk, L.; Awasom, C.; Achu, P.N.; Njinda, A.; Sinha, N.; Rao, P.S.; Agudelo, M.; Nookala, A.R.; et al. Effect of mild-to-moderate smoking on viral load, cytokines, oxidative stress, and cytochrome P450 enzymes in HIV-infected individuals. PLoS ONE 2015, 10, e0122402. [Google Scholar] [CrossRef]
18. Ande, A.; McArthur, C.; Kumar, A.; Kumar, S. Tobacco smoking effect on HIV-1 pathogenesis: Role of cytochrome P450 isozymes. Expert Opin. Drug Metab. Toxicol. 2013, 9, 1453–1464. [Google Scholar] [CrossRef]
19. Rumbaugh, J.A.; Tyor, W. HIV-associated neurocognitive disorders: Five new things. Neurology. Clin. Pract. 2015, 5, 224–231. [Google Scholar] [CrossRef]
20. Sacktor, N.; McDermott, M.P.; Marder, K.; Schifitto, G.; Selnes, O.A.; McArthur, J.C.; Stern, Y.; Albert, S.; Palumbo, D.; Kieburtz, K.; et al. HIV-associated cognitive impairment before and after the advent of combination therapy. J. Neurovirology 2002, 8, 136–142. [Google Scholar] [CrossRef]
21. Cantres-Rosario, Y.M.; Ortiz-Rodriguez, S.C.; Santos-Figueroa, A.G.; Plaud, M.; Negron, K.; Cotto, B.; Langford, D.; Melendez, L.M. HIV Infection Induces Extracellular Cathepsin B Uptake and Damage to Neurons. Sci. Rep. 2019, 9, 8006. [Google Scholar] [CrossRef]
22. Strazza, M.; Pirrone, V.; Wigdahl, B.; Nonnemacher, M.R. Breaking down the barrier: The effects of HIV-1 on the blood-brain barrier. Brain Res. 2011, 1399, 96–115. [Google Scholar] [CrossRef]
23. Atluri, V.S.; Hidalgo, M.; Samikkannu, T.; Kurapati, K.R.; Jayant, R.D.; Sagar, V.; Nair, M.P. Effect of human immunodeficiency virus on blood-brain barrier integrity and function: An update. Front. Cell. Neurosci. 2015, 9, 212. [Google Scholar] [CrossRef] [PubMed]
24. Harrison, J.D.; Dochney, J.A.; Blazekovic, S.; Leone, F.; Metzger, D.; Frank, I.; Gross, R.; Hole, A.; Mounzer, K.; Siegel, S.; et al. The nature and consequences of cognitive deficits among tobacco smokers with HIV: A comparison to tobacco smokers without HIV. J. Neurovirology 2017, 23, 550–557. [Google Scholar] [CrossRef] [PubMed]
25. Chang, L.; Lim, A.; Lau, E.; Alicata, D. Chronic Tobacco-Smoking on Psychopathological Symptoms, Impulsivity and Cognitive Deficits in HIV-Infected Individuals. J. Neuroimmune Pharmacol. Off. J. Soc. Neuroimmune Pharmacol. 2017, 12, 389–401. [Google Scholar] [CrossRef] [PubMed]
26. Bryant, V.E.; Kahler, C.W.; Devlin, K.N.; Monti, P.M.; Cohen, R.A. The effects of cigarette smoking on learning and memory performance among people living with HIV/AIDS. Aids Care 2013, 25, 1308–1316. [Google Scholar] [CrossRef]
27. Wojna, V.; Robles, L.; Skolasky, R.L.; Mayo, R.; Selnes, O.; de la Torre, T.; Maldonado, E.; Nath, A.; Melendez, L.M.; Lasalde-Dominicci, J. Associations of cigarette smoking with viral immune and cognitive function in human immunodeficiency virus-seropositive women. J. Neurovirology 2007, 13, 561–568. [Google Scholar] [CrossRef]
28. Tsima, B.; Ratcliffe, S.J.; Schnoll, R.; Frank, I.; Kolson, D.L.; Gross, R. Is Tobacco Use Associated with Neurocognitive Dysfunction in Individuals with HIV? J. Int. Assoc. Provid. Aids Care 2018, 17, 2325958218768018.
29. Thery, C.; Witwer, K.W.; Aikawa, E.; Alcaraz, M.J.; Anderson, J.D.; Andriantsitohaina, R.; Antoniou, A.; Arab, T.; Archer, F.; Atkin-Smith, G.K.; et al. Minimal information for studies of extracellular vesicles 2018 (MISEV2018): A position statement of the International Society for Extracellular Vesicles and update of the MISEV2014 guidelines. J. Extracell. Vesicles 2018, 7, 1535750. [Google Scholar] [CrossRef] [PubMed]
30. Yuan, D.; Zhao, Y.; Banks, W.A.; Bullock, K.M.; Haney, M.; Batrakova, E.; Kabanov, A.V. Macrophage exosomes as natural nanocarriers for protein delivery to inflamed brain. Biomaterials 2017, 142, 1–12. [Google Scholar] [CrossRef]

31. Colombo, M.; Raposo, G.; Thery, C. Biogenesis, secretion, and intercellular interactions of exosomes and other extracellular vesicles. Annu. Rev. Cell Dev. Biol. 2014, 30, 255–289. [Google Scholar] [CrossRef]
32. Greening, D.W.; Simpson, R.J. Understanding extracellular vesicle diversity-current status. Expert Rev. Proteom. 2018, 15, 887–910. [Google Scholar] [CrossRef]
33. Latifkar, A.; Hur, Y.H.; Sanchez, J.C.; Cerione, R.A.; Antonyak, M.A. New insights into extracellular vesicle biogenesis and function. J. Cell Sci. 2019, 132. [Google Scholar] [CrossRef] [PubMed]
34. Kucharzewska, P.; Belting, M. Emerging roles of extracellular vesicles in the adaptive response of tumour cells to microenvironmental stress. J. Extracell. Vesicles 2013, 2. [Google Scholar] [CrossRef] [PubMed]
35. Welch, J.L.; Stapleton, J.T.; Okeoma, C.M. Vehicles of intercellular communication: Exosomes and HIV-1. J. Gen. Virol. 2019, 100, 350–366. [Google Scholar] [CrossRef]
36. Urbanelli, L.; Buratta, S.; Tancini, B.; Sagini, K.; Delo, F.; Porcellati, S.; Emiliani, C. The Role of Extracellular Vesicles in Viral Infection and Transmission. Vaccines 2019, 7, 102. [Google Scholar] [CrossRef]
37. Kodidela, S.; Ranjit, S.; Sinha, N.; McArthur, C.; Kumar, A.; Kumar, S. Cytokine profiling of exosomes derived from the plasma of HIV-infected alcohol drinkers and cigarette smokers. PLoS ONE 2018, 13, e0201144. [Google Scholar] [CrossRef] [PubMed]
38. Ranjit, S.; Patters, B.J.; Gerth, K.A.; Haque, S.; Choudhary, S.; Kumar, S. Potential neuroprotective role of astroglial exosomes against smoking-induced oxidative stress and HIV-1 replication in the central nervous system. Expert Opin. Ther. Targets 2018, 22, 703–714. [Google Scholar] [CrossRef] [PubMed]
39. Haque, S.; Sinha, N.; Ranjit, S.; Midde, N.M.; Kashanchi, F.; Kumar, S. Monocyte-derived exosomes upon exposure to cigarette smoke condensate alter their characteristics and show protective effect against cytotoxicity and HIV-1 replication. Sci. Rep. 2017, 7, 16120.
40. Hutter, G.; Nowak, D.; Mossner, M.; Ganepola, S.; Mussig, A.; Allers, K.; Schneider, T.; Hofmann, J.; Kucherer, C.; Blau, O.; et al. Long-term control of HIV by CCR5 Delta32/Delta32 stem-cell transplantation. New Engl. J. Med. 2009, 360, 692–698. [Google Scholar] [CrossRef]
41. Gupta, R.K.; Abdul-Jawad, S.; McCoy, L.E.; Mok, H.P.; Peppa, D.; Salgado, M.; Martinez-Picado, J.; Nijhuis, M.; Wensing, A.M.J.; Lee, H.; et al. HIV-1 remission following CCR5Delta32/Delta32 haematopoietic stem-cell transplantation. Nature 2019, 568, 244–248. [Google Scholar] [CrossRef]
42. Vanhamel, J.; Bruggemans, A.; Debyser, Z. Establishment of latent HIV-1 reservoirs: What do we really know? J. Virus Erad. 2019, 5, 3–9. [Google Scholar]
43. Kruize, Z.; Kootstra, N.A. The Role of Macrophages in HIV-1 Persistence and Pathogenesis. Front. Microbiol. 2019, 10, 2828. [Google Scholar] [CrossRef] [PubMed]
44. Van Marle, G.; Church, D.L.; van der Meer, F.; Gill, M.J. Combating the HIV reservoirs. Biotechnol. Genet. Eng. Rev. 2018, 34, 76–89. [Google Scholar] [CrossRef] [PubMed]
45. Wacleche, V.S.; Tremblay, C.L.; Routy, J.P.; Ancuta, P. The Biology of Monocytes and Dendritic Cells: Contribution to HIV Pathogenesis. Viruses 2018, 10, 65. [Google Scholar] [CrossRef] [PubMed]
46. Sung, J.M.; Margolis, D.M. HIV Persistence on Antiretroviral Therapy and Barriers to a Cure. Adv. Exp. Med. Biol. 2018, 1075, 165–185. [Google Scholar] [CrossRef] [PubMed]
47. Sharma, H.; Chinnappan, M.; Agarwal, S.; Dalvi, P.; Gunewardena, S.; O'Brien-Ladner, A.; Dhillon, N.K. Macrophage-derived extracellular vesicles mediate smooth muscle hyperplasia: Role of altered miRNA cargo in response to HIV infection and substance abuse. Faseb J. Off. Publ. Fed. Am. Soc. Exp. Biol. 2018, 32, 5174–5185. [Google Scholar] [CrossRef]
48. Tang, N.; Sun, B.; Gupta, A.; Rempel, H.; Pulliam, L. Monocyte exosomes induce adhesion molecules and cytokines via activation of NF-kappaB in endothelial cells. Faseb J. Off. Publ. Fed. Am. Soc. Exp. Biol. 2016, 30, 3097–3106. [Google Scholar] [CrossRef]
49. Kodidela, S.; Wang, Y.; Patters, B.J.; Gong, Y.; Sinha, N.; Ranjit, S.; Gerth, K.; Haque, S.; Cory, T.; McArthur, C.; et al. Proteomic Profiling of Exosomes Derived from Plasma of HIV-Infected Alcohol Drinkers and Cigarette Smokers. J. Neuroimmune Pharmacol. Off. J. Soc. Neuroimmune Pharmacol. 2019.