

LETTER TO THE EDITOR

Potential Effects of COVID-19 on the Release of Cancer Cell-derived Exosomes and Bone Metastasis

Van-Thanh Duong^{1†}, Manh Tien Tran^{2†*}

¹Department of Anatomy, Pusan National University School of Medicine, Yangsan, Gyeongsangnam-do 50612, Republic of Korea

²Department of Dental Pharmacology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama 700-8525, Japan

[†]These authors contributed equally to this work.

Dear Editor,

In this letter, we seek to dissect and summarize the crucial effects of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), on accelerating the release of cancer cell-derived exosomes, thereby promoting cancer metastasis in bone.

COVID-19, which is a highly contagious infection causing acute respiratory syndrome, has severely affected people's lives worldwide^[1]. In addition to the investigations into the specific characteristics of SARS-CoV-2, understanding the fundamental physiological and immunological processes underlying the clinical manifestations of COVID-19 is crucial for the development of effective therapies. The respiratory droplets-mediated transmission of the SARS-CoV-2 virus is mainly achieved via person-to-person contact. The most common symptoms caused by COVID-19 are fever, dry cough, dyspnea, headaches, sore throat, and rhinorrhea^[1]. It has been suggested that the immune system plays a pivotal role in controlling COVID-19 progression^[2] by which the adaptive immune cells are involved in SARS-CoV-2 virus clearance, the innate immune cells could promote disease progression. For instance, interleukin (IL)-6 produced by macrophages was shown to trigger the excessive inflammation, which could deteriorate the recovery of COVID-19 patients by eliciting macrophage activation syndrome^[3]. It was reported that inhibition of IL-1 and IL-6 cytokines and/or receptors in the patients with over-activated macrophages could be a promising therapeutic tool for the treatment of COVID-19^[4]. Besides, it was demonstrated that SARS-CoV-2 infection significantly increased transforming growth factor beta1 (TGFβ1) expression at both mRNA and protein levels via a papain-like protease (PLpro)-dependent mechanism, thereby enhancing the expression of TGFβ1-induced genes^[5,6]. Particularly, TGFβ1, which could be activated by PLpro via ROS/p38 MAPK/STAT3 pathway both *in vitro* and *in vivo* with a direct pulmonary injection^[7], regulates the host immune responses with the help of a COVID-19-induced cytokine storm such as tumor necrosis factor (TNF), IL-1β and IL-6^[8], which leads to the immune exhaustion. In addition, another study has confirmed that TGFβ overexpression was found in the lung samples of the severe acute respiratory syndrome (SARS) patients, and the OT-101-induced knockdown of TGFβ expression led to the suppression of SARS-CoV-1 and SARS-CoV-2 replication *in vitro*^[9].

Exosomes arising from the membranes of multivesicular bodies (MVBs) are cup-shaped with diameters ranging from 50 nm to 150 nm^[10]. Exosomes contain a variety of bio-molecules such as proteins, lipids, nucleic acids (mRNAs, non-coding [nc] RNAs and DNA), and metabolites^[10-12]. The cargos in exosomes serve as the external stimuli for the recipient cells, thereby modifying the biological features of the recipient cells

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***CORRESPONDING AUTHOR**

Manh Tien Tran
E-mail: trantienmanh1508@gmail.com.

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by both autocrine and paracrine signaling transductions^[13]. In cancer, exosome-mediated transfer of different cargos may enhance cancer progression and metastasis. For example, miR-17, miR-19a, miR-21, miR-126, and miR-149 expression exhibited a positive correlation with the progression of metastatic sporadic melanoma^[14]. In addition, the oncogenic receptor EGFRvIII was shown to be transported between glioma cells with the aid of exosomes, leading to the transfer of oncogenic activity as well as transforming the phenotype and EGFRvIII-dependent transcription^[15]. Interestingly, a previous study has shown that patient-derived exosomes contained SARS-CoV-2 RNA, suggesting that it was possible SARS-CoV-2 virus exploited the endocytosis route to spread infection^[16].

Bone metastasis is characterized by the dissemination of metastatic cancer cells from the primary sites such as lung, breast, and prostate, to the bone milieu (BM). Once metastasized into the BM, cancer cells normally enter a long-lived dormant state, and remain quiescent for years. Cancer cell dormancy and development in bone are controlled by the interactions amongst cancer cells and bone cells (osteoblasts, osteoclasts, and osteocytes), and immune cells in the local BM^[17]. A growing line of evidence suggests that tumor-derived exosomes contribute to establishing an apt microenvironment to create the pre-metastatic niche for colonization of metastatic cancer cells^[18-21]. However, the detailed mechanisms that cancer cell-derived exosomes regulate the functional communications among cancer cells, bone cells, and immune cells in the local BM remain unclear.

In view of the above, we propose research directions as follows:

(1) To examine the effects of pro-inflammatory factors (IL-6, TNF, IL-1 β , etc.) released by the innate and adaptive immune cells on the production of cancer cell-derived exosomes in the local BM and on bone metastasis in the cancer patients infected with SARS-CoV-2; and

(2) To investigate whether cancer cell-derived exosomes carry and transmit SARS-CoV-2 mRNA to the bone cells and immune cells in the local BM, and how the bone cells and immune cells could be affected by SARS-CoV-2-rich exosomes.

We are anticipating that the above-mentioned research avenues could be acted upon as soon as possible so that we will further understand the severe effects of COVID-19 on the patients with cancers, especially bone metastasis.

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