

## Editorial Commentary: Challenge of Non–AIDS-Defining Cancers (NADCs), Focusing on Trans-Activation Response Element (TAR) RNA Embedding Exosomes

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Globally, 37.9 million people were living with HIV at the end of 2018 (Organization, 2018). Cancer is a major cause of mortality and morbidity in AIDS patients and chronically HIV-infected people. With the aid of combination Antiretroviral Therapy (ART), people living with HIV (PLWH) have a longer life span. However, because the virus is not completely eradicated, PLWH under antiretroviral therapy may have an increased risk of Non-AIDS-Defining Cancers (NADCs) (Deeks *et al.*, 2013). As defined by NCI, NADCs include Hodgkin lymphoma and cancers of the mouth, throat, liver, lung and anus. Besides HIV infection, other factors, such as older age, infection with other viruses and heavy alcohol or tobacco use, may also increase the risk of developing an NADC (Institute, 0000). Patients with HIV/AIDS are reported to have a two to four-fold increase in risk for head and neck cancers (Powles *et al.*, 2009). Compared with uninfected subjects, the risk of HIV-infected patients with lung cancer has several folds increased (Chaturvedi *et al.*, 2007). Multiple mechanisms contribute to this phenomenon, including longer life expectancy, control of oncogenic infections and exposure to carcinogens (Wang *et al.*, 2014). However, the underlying mechanism for development and progression of certain NADCs remains obscure.

A recent article published in *Nat Commun.* (Nov 2, 2018), entitled “*Exosomes derived from HIV-1-infected cells promote growth and progression of cancer via HIV TAR RNA*”, Jin’s group exhibited an effort to meet this challenge (Chen *et al.*, 2018). This research enrolled 18 HIV-positive patients and discovered how two aggressive cancers used exosomes excreted from HIV-infected T cells to promote their cancer aggressiveness. Three key messages are present in this study based on the results: First, HIV-infected patients even under ART treatment contain circulating pro-tumor exosomes, in which HIV-specific exosome cargo components are able to promote proliferation, migration and invasion and induce the expression of proto-oncogenes in Head and Neck Squamous Cell Carcinoma (HNSCC) and lung cancer cells in vitro and stimulate xenograft tumor growth in vivo. Second, the HIV Transactivation

Response (TAR) element RNA is found to be overwhelmingly produced in exosomes from HIV-infected patient sera. TAR is a precursor of several HIV-encoded miRNAs that forms a stem-loop folding structure in the nascent transcript and facilitates binding of the viral transcriptional Trans-activator (Tat) protein to enhance transcription initiation and elongation of HIV. Most importantly, the HIV TAR RNA in HIV-infected T-cell exosomes is responsible for the expression of the proto-oncogene *FOS* and TLR3-associated induction of Interferon-Stimulated Genes (ISGs) in cancer cells, depending on the loop/bulge region of the molecule. Finally, a nucleotide aptamer called R06, which forms a face-to-face “kissing” structure to block the function of TAR RNA, attenuates gene expression and inhibits progressive behaviors of cancer cells when transfected into HIV-infected T-cell exosomes (Beaurain *et al.*, 2003). This is the first report addressing whether HIV-infected cells are involved in the development and progression of NADCs and identified the critical role of the loop/bulge region of TAR in the pathological event, although further investigation of the TAR RNA in the HIV/AIDS infection and transmission is needed.

Exosomes are a type of extracellular vesicles about 30–120 nm in diameter released in body fluids by almost all types of cells (Akers *et al.*, 2013). There are various proteins and RNA in exosomes (Vlassov *et al.*, 2012). Interestingly, the data from the analysis by Mass Spectrometry showed that, compared to exosomes from uninfected T-cells, exosomes from HIV-1-infected T-cells are enriched in histones, RNA-binding proteins, Cdks and Src family kinases (Barclay *et al.*, 2019). Consistent with the observation in Jin’s group on HNSCC and lung cancer, it has been found that exosomes isolated from HIV-1-infected cells promote the growth and progression of cervical cancer as well (Li *et al.*, 2019). In this study, miR-155-5p was identified as the culprit molecule in exosomes to promote the pathogenic progress of HIV-1-associated cervical cancer.

TAR RNA, which has a highly folded stem-bulge-loop structure, plays an important role in the molecular

interaction between a virus and its host (Bannwarth and Gatignol, 2005). Abundance of TAR RNA exists up to 63% in exosomes from HIV-1-infected patients (Hladnik *et al.*, 2018), suggesting the importance of the molecule in the pathogenic event. Thus, designing small molecule inhibitors or mimetic peptides to block the function of TAR RNA may be clinically significant in treating the patients. Alternatively, the CRISPR-Cas9 method can be employed to abolish TAR RNA in exosomes (Sharma, 2019). In addition, development of a new assessment method for TAR RNA in HIV associated cancer patients' biopsies is urgently needed (Sharma, 2019).

Based on updated "Guidelines for Cancer in People Living with HIV" in 2019, PLWH should be offered the same cancer therapies as HIV-negative individuals (Reid *et al.*, 2018). In the US, the life expectancy for most PLWH on ART now approaches that of the general population (Ray *et al.*, 2010). Cancer is the leading cause of death among this population in developed countries (Morlat *et al.*, 2014). In developing countries, NADCs are common among long-term surviving HIV-infected patients not requiring therapy or without access to therapy (Pantanowitz and Dezube, 2009). Half of Asian NADC patients were aged 40-59 years and had advanced-stage disease at diagnosis (Nagata *et al.*, 2018). The proportion of PLWH who are age 65 or older is expected to triple by 2030; it is likely to change the landscape of both ADCs and NADCs in this population (Shiels *et al.*, 2018). Apparently, early detection and effective treatment of oncogenic viruses may be the best way to prevent the incidence of cancers among PLWH.

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