Pyruvate kinase muscle type 2 and human immunodeficiency virus type 1 replication: the regulatory function on HIV-1 reverse transcription beyond glycolysis

Clinical Pharmaceutical Sciences, HIGO Program Four-year Course,
Department of Environmental and Molecular Health Sciences
Kumkum Rahman Mouree

HIV-1 is a retrovirus representing a causative agent of well-defined clinical conditions termed as AIDS. Inside human host cells, the virus completes several stages of its life cycle. Reverse transcription represents a vital stage which is completely dependent on host factors such as lysyl-tRNA synthetase (LysRS) and $tRNA^{Lys3}$, and thus a potential target for antiretroviral drug therapy.

Several studies of purified HIV-1 virions have shown that in addition to viral proteins encoded by viral genome, host proteins are found inside virions and modulate the viral infectivity. Therefore, direct analysis of those host proteins inside virions might represent a key approach to explicit the viral replication capacity. For this purpose, we performed two-dimensional gel electrophoresis of purified viral preparation to separate individual viral and host proteins, and identified each spot by MALDI-TOF mass spectrometry and then detected pyruvate kinase muscle type 2 (PKM2) inside virions. The virion-packaged PKM2 significantly reduces the viral infectivity by affecting the reverse transcription efficiency in target cells.

In our study, compared with the control virus, enhanced expression of PKM2 in HIV-1-producing cells led to a higher incorporation level of PKM2 into progeny virions without affecting the viral maturation process. The high-level-PKM2-packaging viruses showed decreased levels of both reverse transcription products and cellular tRNALys3 packaging, suggesting that the shortage of intravirion $tRNA^{Lys3}$ suppresses reverse transcription efficiency in target cells. Interestingly, the enhanced expression of PKM2 in HIV-1-producing cells also suppressed the virion packaging of other nonpriming cellular tRNAs such as $tRNA^{Lys1, 2}$ and $tRNA^{Asn}$, which are known to be selectively packaged into virions, without affecting the steady level of the cytoplasmic pool of those tRNAs in HIV-1-producing cells, suggesting that PKM2 specifically impedes the selective incorporation of tRNAs into virions. Since virion packaging of $tRNA^{Lys3}$ occurs as a result of selective interaction among LysRS and viral polyprotein Gag-pol, PKM2 might hamper any of such selective interactions to suppress virion packaging of $tRNA^{Lys3}$ to provide its crucial priming function.

Our current study thus unveils a distinct regulatory function of PKM2 and provides a new option for therapeutic intervention targeting HIV-1-host interaction.