Small molecule compounds inhibit Vpu mediated down-regulation BST-2

Shan Cen, Zeyun Mi, Quan Zhang, Jinming Zhou, Xiaoyu Li and Jiwei Ding
Chinese Academy of Medical Sciences, China

Background: BST-2(Tetherin/CD317) has been recently recognized as a potent restriction factor that inhibits the release of HIV-1 particles from infected cells. HIV-1 Vpu induces the degradation of BST-2 and allows virus escape from the restriction. Therefore, blocking Vpu-mediated down-regulation of cell surface BST-2 provides clearly an opportunity for developing anti-HIV-1 drugs.

Method: In this study, a cell-based ELISA assay was used to screen for small molecule compounds that restore cell surface BST-2 in the presence of Vpu. Co-IP, BRET, cell image and other techniques were performed to study the mechanism of positive compounds.

Results: In this study, we identified two small molecule compounds IMB-AZ and IMB-LA, both of which can restore cell surface BST-2 in a Vpu-dependent manner. Interestingly, the compounds had no effect on the degradation of IFNAR1 induced by IFN, suggesting that their abilities to block BST-2 degradation most unlikely resulted from a general inhibition of lysosome degradation pathway. Mechanism study revealed that IMB-AZ specifically inhibit Vpu-induced ubiquitination of BST-2 without interrupting the formation of Vpu-β-TrCP complex. Unlike IMB-AZ, the treatment of IMB-LA resulted in accumulation of BST-2 within CD63-containing endosomal compartments, suggesting that IMB-LA may impair the translocalization of BST-2 to lysosomes and consequently inhibit the degradation of BST-2. Furthermore, the results of viral infectivity assay demonstrated that both of IMB-AZ and IMB-LA inhibit the release of HIV-1 particles and the infectivity of progeny virions in cell lines expressing BST-2.

Conclusion: In summary, results here in demonstrated that both of IMB-AZ and IMB-LA could specifically inhibit the degradation of BST-2 induced by Vpu, and impair HIV-1 replication in a BST-2 dependent manner, suggesting IMB-AZ and IMB-LA have potent potential to develop a new anti-HIV drug.

shancen@hotmail.com

A novel “priming-boosting” strategy for immune interventions in cervical cancer

Mrs shujie
Cancer Biology Research Center, Tongji Medical College, China

Despite the encouraging development of a preventive vaccine for human papillomavirus (HPV), it cannot improve ongoing infections. Therefore, a new vaccine is urgently needed that can prevent and treat cervical cancer, and cure pre-cancerous lesions. In this study, we constructed two peptide-based vaccines. The first was a short-term, long-peptide (ST-LP) vaccine that simultaneously targeted three key carcinogenic epitopes (E5-E6-E7) on HPV16. We tested this vaccine in murine TC-1 cells infected with a recombinant adeno-associated virus (rAAV) fused with HPV16E5 DNA (rTC-1 cells), which served as a cell model; we also tested it in immune-competent mice loaded with rTC-1 cells, which served as an ectopic tumor model. The ST-LP injections resulted in strong, cell-mediated immunity, capable of attacking and eliminating abnormal antigen-bearing cells. Furthermore, to prolong immunogenic capability, we designed a unique rAAV that encoded the three predicted epitopes for a second, long-term, long-peptide (LT-LP) vaccine. Moreover, we used a new immune strategy of continuous re-injections, where three ST-LP injections were performed at one-week intervals (days 1, 8, 15), then one LT-LP injection was performed on day 120. Our *in vitro* and *in vivo* studies revealed that this strategy could boost the immune response to produce longer and stronger protection against target cells, and mice were thoroughly protected from tumor growth. Our results showed that priming the immune system with the ST-LP vaccine, followed by boosting the immune system with the LT-LP vaccine could generate a rapid, robust, durable cytotoxic T-lymphocyte response to HPV16-positive tumors.

sjliao@tjh.tjmu.edu.cn