Type: Poster Presentation

Final Abstract Number: 64.025
Session: Virology and Viral Infections (Non-HIV) II
Date: Saturday, April 5, 2014
Time: 12:45-14:15
Room: BallroomType

Decreased frequency of regulatory T cells is associated with severe immunopathology in hepatitis A

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Background: $FoxP3^{+}CD4^{+}CD25^{+}$ regulatory T (Treg) cells are known to control immune responses against self and foreign antigens, but their role in acute viral infection remains to be elucidated. Herein, we investigated frequency of Treg cells in acute hepatitis A (AHA) and their implications in immunopathology.

Methods & Materials: Forty-nine patients, who were diagnosed with AHA and hospitalized in Ilsan Paik Hospital or Chung-Ang University Hospital, were recruited in this study. All patients were seropositive for anti-HAV IgM, and all had clinical features of acute hepatitis. Peripheral blood samples at the acute stage were collected on the day of admission from all of the 49 patients. Follow-up sampling was performed at the subacute or convalescent stage. Frequency and immunophenotypes of Treg cells was analyzed in the peripheral blood using multicolor flow cytometry. Suppressive activity of Treg cell population was determined by assessing anti-CD3/CD28-stimulated proliferation of Treg-depleted PBMCs with or without adding-back of the depleted cells. Apoptosis of Treg cells was also evaluated by flow cytometery.

Results: Frequency of circulating Treg cells was reduced during AHA. In addition, *in vitro* suppressive activity of Treg cell population was compromised, which was related with decreased frequency of Treg cells. Both decreased Treg cell frequency and attenuated suppressive activity was closely associated with the severity of liver injury. Treg cells of AHA patients contained lower percentage of Ki-67^{+} population and expressed higher level of Fas compared to healthy subjects. In AHA patients, apoptotic Treg cells were increased and *in vitro* stimulation of Fas resulted in reduction of Treg cell frequency.

Conclusion: Pool size of circulating Treg cells was contracted in AHA. The contracted pool size of Treg cells was associated with attenuated suppressive activity of Treg cell population and severe immunopathology, indicating a role of Treg cells in the control of immunopathology in acute viral hepatitis.

http://dx.doi.org/10.1016/j.ijid.2014.03.1355

Type: Poster Presentation

Final Abstract Number: 64.026
Session: Virology and Viral Infections (Non-HIV) II
Date: Saturday, April 5, 2014
Time: 12:45-14:15
Room: Ballroom

The multi-targeted kinase inhibitor Sorafenib inhibits Enterovirus 71 IRES activity

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Background: The activation of ERK and p38 signal cascade in host cells has been demonstrated to be essential for picornavirus enterovirus 71 (EV71) replication and up-regulation of virus-induced cyclooxygenase-2(COX-2)/prostaglandins E_2 (PGE_2) expression. The aim of this study was to examine the effects of sorafenib, a clinically approved anti-cancer multi-targeted kinase inhibitor, on the propagation and pathogenesis of EV71, with a view to its possible mechanism and potential use in the design of therapy regimes for Hand foot and mouth disease (HFMD) patients with life threatening neurological complications.

Methods & Materials: The yield of infectious progeny virus was measured by virus plaque assay. Quantitative reverse transcription polymerase chain reaction (q-RT-PCR) and Western blot assays were used to detect genomic RNA and the VP1 capsid protein of EV71. The activity of the EV71 internal ribosomal entry site (IRES) was assayed by linking it to a luciferase reporter gene. Measurement of the effect of sorafenib on EV71-induced cytopathic effect (CPE) and the activation of ERK and p38, was carried out by phase contrast microscopy and Western blot assay respectively.

Results: The yield of infectious progeny virus was measured by virus plaque assay. Quantitative reverse transcription polymerase chain reaction (q-RT-PCR) and Western blot assays were used to detect genomic RNA and the VP1 capsid protein of EV71. The activity of the EV71 internal ribosomal entry site (IRES) was assayed by linking it to a luciferase reporter gene. Measurement of the effect of sorafenib on EV71-induced cytopathic effect (CPE) and the activation of ERK and p38, was carried out by phase contrast microscopy and Western blot assay respectively.

Conclusion: Overall, this study shows that sorafenib strongly inhibits EV71 replication at least in part by regulating viral IRES-dependent translation of viral proteins. To our knowledge, this is the first report that investigates the mechanism by which sorafenib inhibits EV71 replication.

http://dx.doi.org/10.1016/j.ijid.2014.03.1356