PERSISTENT HEPATITIS C VIRUS (HCV) INFECTION IMPAIRS HCV-SPECIFIC CYTOTOXIC T CELL REACTIVITY THROUGH MCL-1/BIM IMBALANCE DUE TO CD127 DOWN-REGULATION.

Juan R Larrubia, Megha U Lokhande, Joaquín Miquel, Silvia García-Garzón, Alejandro González-Praetorius y Eduardo Sánchez-de-Villalobos.

Translational Hepatology Unit, Guadalajara University Hospital. University of Alcalá, Guadalajara, Spain

BACKGROUND AND AIMS

In persistent hepatitis C virus (HCV) infection, HCV-specific cytotoxic T lymphocyte (CTL) reactivity is impaired and this affects HCV control. Interleukin-7 receptor (CD127) expression on these cells could regulate CTL reactivity through Mcl-1/Bim balance modulation. Bim is a pro-apoptotic molecule blocked by the action of Mcl-1.

METHODS

Mcl-1/Bim expression and T cell reactivity on HCV-specific CTLs were compared according to CD127 phenotype. Peripheral blood lymphocytes (PBL) from HLA-A2+ HCV+ patients were obtained. HCV-specific CTLs were visualized by staining PBL with anti-CD8 and HLA-A2/peptide pentameric complexes (pentamer). Mcl-1/Bim/CD127 phenotype of HCV-specific CTLs was tested by staining detectable CD8+pentamer+ cells with anti-Mcl-1/Bim/CD127 antibodies. HCV-specific CTL proliferation ability after specific in vitro challenge was tested in the presence and absence of pancaspase inhibitor z-VAD-fmk. All stained cells were analysed by flow cytometry.

RESULTS

CD127low-expressing HCV-specific CTLs associated with high HCV viremia, while CD127high correlated with undetectable viral loads (p<0.001) (Fig.1). Directly ex vivo, pentamer+ cell frequency was similar according to CD127 expression level. Nevertheless, CD127low pentamer+ cell proliferation after specific in vitro challenge was impaired (p<0.05), although partially corrected by z-VAD-fmk treatment (p<0.05) (Fig.2). Mcl-1 expression was low directly ex vivo (p<0.01), and Bim was up-regulated after antigen encounter (p<0.05) of CD127low pentamer+ cells (Fig.3). The ex-vivo difference between Mcl-1- and Bim expression on pentamer+ cells correlated positively with CD127 expression level (p<0.001) and with pentamer+ cell reactivity (p<0.05) (Fig.4).

CONCLUSIONS

A low ex vivo Mcl-1 expression and Bim up regulation after antigen encounter are involved in CD127low HCV-specific CTL hyporeactivity during chronic infection, but it can be overcome by apoptosis blockade.