recognized by RIG-I and MDA5, further increasing the innate immune response against HCV. OAS1 means, 2′−5′ oligoadenylate synthase (57,58).

## c. HCV Inhibits Immune Responses

HCV impairs immune response by inhibiting innate immune response, and by inhibiting adaptive immune response. HCV evades innate immune response by damaging TLRs. HCV evades adaptive immune response by provoking exhaustion of T cells.

This is about *innate immunity*. HCV's N3/4A protease catalyzes the cleavage and inactivation of host cell proteins that sense the presence of HCV's RNA (59). HCV's proteins and HCV's nucleic acid are sensed by TLRs, where the proteins are sensed by TLR2 and TLR4, and the RNA is sensed by TLR3, TLR7, and TLR9. TLR3 detects double-stranded RNA intermediates that exist during replication of the HCV genome. However, as stated above, N3/4A protease inactivates host cell proteins that mediate innate immune response against HCV. In detail, the N3/4A protease inactivates host cell proteins called MAVS and TRIF.

This concerns *T-cell exhaustion*. Yamada et al. (60) characterized T-cell exhaustion as a mechanism where viruses "subvert host immunity." The mechanisms of T-cell exhaustion concern adaptive immune response. HCV-infected patients have higher PD-1 expression on $CD4^+$ T cells and $CD8^+$ T cells, compared with healthy human subjects. Also, in patients with chronic HCV, NK cells expressed higher levels of PD-1, consistent with their greater functional incompetence and less mature differentiation state (61). Treatment with HCV-drugs consequently results in lower PD-1 expression, that is, expression back to normal low levels.

Exhaustion of $CD8^+$ T cells that follows a pattern of progressive loss of function, that is, decreased IL-2 and TNF-alpha secretion, followed by loss of IFN-gamma production. Exhaustion culminates in loss of cytolytic activity of $CD8^+$ T cells (62). Chronic exposure of viral antigens to T cells provokes increased expression of PD-1 by the T cell (63).

In chronic infection, HCV-specific T cells are focused on only a few HCV antigens, and these T cells decline to such low numbers that they are often undetectable in the blood. The few HCV-specific T cells that are detectable display an

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