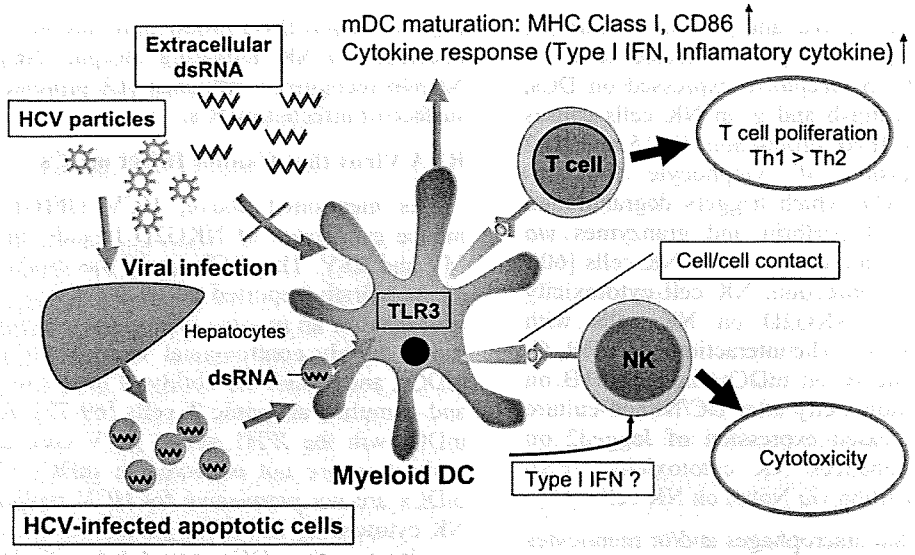

Fig. (3). HCV-infected apoptotic cells, but not HCV particles, regulate mDC function to activate NK cells and T cells. The HCV JFH1 strain does not directly stimulate mDCs or pDCs. In this case, pDCs and mDCs do not directly respond to the RNA virus. Our recent finding is that dsRNA in HCV-infected apoptotic vesicles is an immune-stimulator for mDCs that triggers the innate system for the activating T cell (Th1 dominant) and NK cells. Cell/cell contact between mDCs and NK cells is indispensable to increased NK cell cytotoxicity.

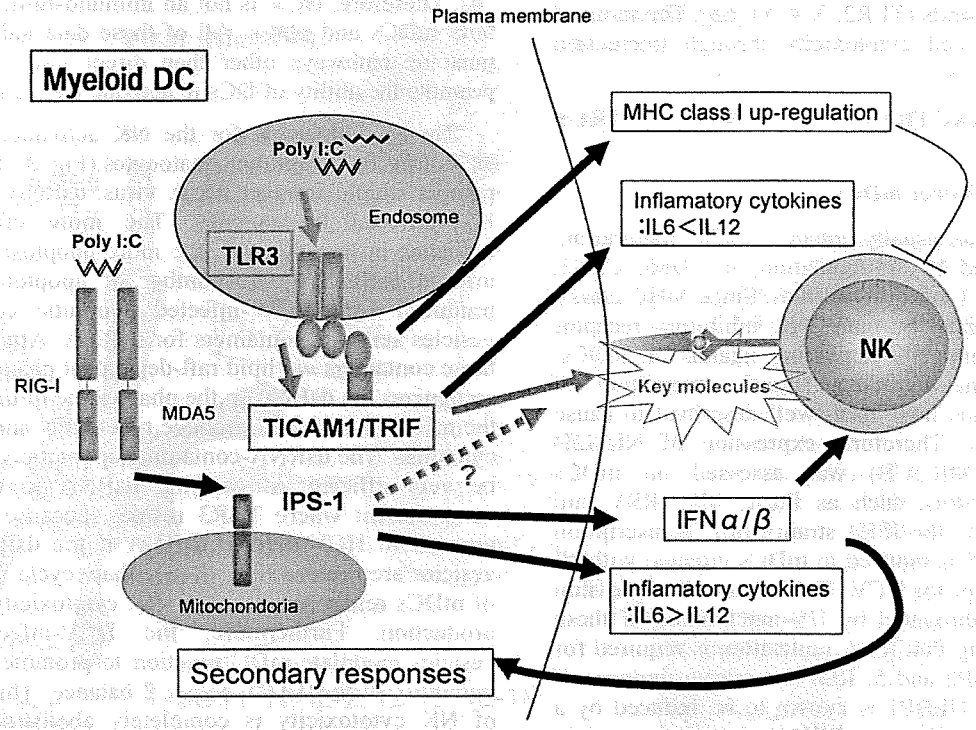

Fig. (4). The TLR3/TICAM1 signal leads to expression of unknown molecules on mDC, which activate NK cell *via* cell/cell contact. Among the three poly I:C receptors (TLR3, RIG-I and MDA5), the TLR3/TICAM1 signal plays an important role in regulating mDC capacity to activate NK cells. This mDC-mediated NK activation is dependent on the direct interaction of mDC and NK cells. Besides IL-15, there must be other key molecules that are induced on mDC by the TLR3/TICAM1 signal to activate NK cells because IL-15 is normally induced by poly I:C in TICAM-/- mice. NK activity is also regulated by type I IFN mediated by MDA5/IPS-1 pathway. Although IL-12 is produced mainly by the TICAM1 signal, IL-12 is not a functional entity that can enhance NK cytotoxicity by poly I:C-stimulated mDCs.

through poly I:C-stimulated DCs requires cell/cell contact. Although type I IFN is a key molecule regulating NK activation, the IFNa response in TICAM1 -/- mice is comparable to that in wild type mice. This is because another poly I:C receptor, MDA5, recognizes poly I:C and leads to IFNa production [19].

Poly I:C-dependent IL-12 production is impaired in TICAM1 -/- mice [13,19]. However, neutralization of IL-12 with anti IL-12 antibodies does not affect dsRNA-induced NK activation [13]. All of these data suggest that the TLR3/TICAM1 signal leads to up-regulation of a certain NK-activating ligand on mDCs. Lucas *et al.* showed that type I IFN secretion and trans-presentation of IL-15 by

mDCs are crucial to DC-mediated NK activation in response to poly I:C [14]. However, induction of IL-15 by mDCs is normal after stimulation with poly I:C in TICAM1-/- mice (unpublished data). We are now searching for the unknown molecules that regulate NK activation on mDCs (Fig. 4), other than IL-15. This unidentified factor may contribute to elucidation of the way NK cells are activated by mDCs during HCV infection.

CONCLUSION

NK cells are principal components of innate immunity and play a key role in early immune responses to viruses. The pathway mediating NK activation has been precisely examined *in vivo* by MCMV (DNA virus) infection. However, the receptors that sense virus-derived DNA are still unknown, except for TLR9 and DAI [75]. Many systems (such as TLR3, RIG-I, MDA5, TLR7 and TLR8) have been shown to trigger innate immunity against virus-derived RNA, but the mechanism of NK cell activation is less studied in RNA virus infection than in DNA virus infection. pDCs, mDCs, macrophages, monocytes and other cells invaded by RNA viruses presumably constitute a complicated network that activates NK cells. The tropism of RNA viruses appears to be the determinant of the mechanisms by which NK cells participate in innate immunity.

ACKNOWLEDGEMENTS

We thank all the past and present members of the Seya lab and, in particular, Shingai M. and Akazawa T. We also thank Dr. Wakita T. for the gift of the *in vitro* system to propagate the JFH1 strain.

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Received: November 13, 2008 Revised: December 26, 2008 Accepted: January 6, 2009