

Role natural killer group 2D-ligand interactions in hepatitis B infection

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Author contributions: Pollicino T and Koumbi L contributed to this paper.

Conflict-of-interest: I accept responsibility for the contents of the amended manuscript and I affirm that there is no conflict of interest.

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Received: January 28, 2015

Peer-review started: January 28, 2015

First decision: February 7, 2015

Revised: February 17, 2015

Accepted: March 16, 2015

Article in press: March 18, 2015

Published online: April 28, 2015

Abstract

Hepatitis B virus (HBV) infection is the leading cause of liver disease and hepatocellular carcinoma (HCC) worldwide, in spite of prophylactic vaccination and antiviral treatment modalities. The immunopathogenesis of HBV infection has been intensively studied and is

propelled by complex interactions between the virus and the host immune system. Natural killer group 2D (NKG2D) is a well-characterized activating receptor, expressed on natural killer (NK) cells, NK T cells and CD8⁺ cytotoxic T cells. This receptor is present in both humans and mice and binds to a diverge family of ligands that resemble the MHC-class I molecules. Increasing evidence shows that NKG2D-ligand interactions are critical in the establishment of HBV persistence and the development of liver injury and HCC. The expression of NKG2D ligands depends on the presence of several polymorphisms and is also modulated post-transcriptionally by HBV. While it is known that HBV circumvents host's innate immunity *via* the NKG2D pathway but the exact mechanisms involved are still elusive. This letter discusses previous accomplishments on the role of NKG2D ligand regulation in the development of chronic HBV, liver injury and HCC.

Key words: Hepatitis B virus; Natural killer group 2D receptor; Natural killer cells; MHC class I polypeptide-related chain A; Hepatocellular carcinoma

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Core tip: Hepatitis B virus (HBV) infection is the leading cause of liver disease and hepatocellular carcinoma (HCC) worldwide. HBV persistence involves complex interactions between the virus and the immune system of the host. Natural killer group 2D (NKG2D) is an activating receptor, expressed on natural killer (NK), NK T and CD8⁺ T cells. NKG2D-ligand interactions are critical in the establishment of chronicity and the development of liver injury and HCC. However, the exact mechanisms involved are still elusive. Here previous studies are discussed on how HBV modulates the NKG2D activity to result in viral clearance, susceptibility to liver injury and tumour evasion.

Pollicino T, Koumbi L. Role natural killer group 2D-ligand

interactions in hepatitis B infection. *World J Hepatol* 2015; 7(6): 819-824 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v7/i6/819.htm> DOI: <http://dx.doi.org/10.4254/wjh.v7.i6.819>

INTRODUCTION

Despite the availability of an effective vaccine and significant progress in antiviral therapy, hepatitis B virus (HBV) remains a serious global health problem. Currently about one-third of the world's population is having markers of current or past infection, far exceeding the numbers of people infected with human immunodeficiency virus and hepatitis C virus together^[1]. Infection with HBV can cause a wide spectrum of clinical manifestations, ranging from asymptomatic infection to acute self-limiting or fulminant hepatitis, or chronic infection (CHB), which is presented as distinct immunological stages, including immune tolerance and immune activation phases. CHB infection may eventually progress to chronic liver injury, cirrhosis or hepatocellular carcinoma (HCC)^[2]. The risk of HCC in chronic infection is 100-fold higher compared with non-carriers and is directly proportional to high levels of HBV replication^[3].

Most healthy adults raise effective immune responses against HBV that clear the virus. The adaptive immune system mounts a multiprolonged immune response, but its effectiveness depends on the quality of the earlier innate immune response that begins within hours of infection. Natural killer (NK) cells are enriched markedly in the liver and play a pivotal role in self-limiting infection. In addition to the direct killing of viral-infected cells without antigen-specific priming, NK cells regulate the adaptive immune response by producing interferon (IFN)- γ , tumor necrosis factor (TNF)- α and immunoregulating cytokines. In acute HBV infection of primates and humans, NK activity has been positively correlated with viral clearance^[4-6] while IFN- γ production by NK cells has been shown to contribute to the initial control of infection^[5,7-9]. In CHB infection, the function and numbers of intrahepatic NK cells are reported to be higher in the immunotolerant stage than in the immunoactive stage and are accompanied with an increase of HBV-specific T cells and low viremia^[10-12]. High NK cell activity early in infection and in the immunotolerant stage reflects the time for the host to mount efficient adaptive response. However, NK cells also negatively regulate specific antiviral immunity in CHB infection by contributing in the liver inflammation through TNF-related apoptosis-inducing ligand- and Fas-mediated death^[13,14] and by the direct killing of HBV-specific CD8⁺ T cells, which triggers the recruitment of inflammatory cells that sustain and amplify the hepatic damage^[15,16]. NK T cells comprise about one-third of intrahepatic T cells and are known to contribute to the outcome of HBV infection. They express T cell receptors (TCR) but, unlike conventional T cells, recognize lipid-based antigens

presented by the major histocompatibility complex (MHC)-like molecule CD1d. HBV infection has been shown to induce alterations in CD1d expression and NK T activation in CHB patients^[17]. Moreover, NK T cells are shown to regulate NK cell activation *via* the production of cytokines IFN- γ and interleukin 4 (IL-4) in the livers of HBV-transgenic mice^[18].

The effector functions of NK cells are determined by the dynamic and coordinated balance of activating and inhibitory signals through their array of receptors. A well characterized activating receptor expressed in all NK cells is the natural killer group 2D (NKG2D), a type II transmembrane-anchored glycoprotein that plays a key role in immune mediated diseases^[19,20]. In addition to NK cells, it is expressed on the surface of NK T cells, activated CD8⁺ T lymphocytes, γ/δ T cells, and some myeloid cells^[21,22]. NKG2D receptor binds to a diverge family of ligands that are distantly related homologues to MHC class I molecules. In contrast to classical MHC molecules, NKG2D ligands (NKG2DL) do not require association with β_2 microglobulin for expression or function, and do not bind antigenic peptides^[23]. In humans, these proteins are divided into two families: the MHC class- I polypeptide-related chain (MIC) protein family that contains MICA and MICB; and the cytomegalovirus UL16-binding proteins (ULBP) family, which consists of five members, ULBP1-4 and RAET1G^[24]. In mice, there are five retinoic acid early transcript 1 (RAET-1) proteins, H60 and murine ULBP-like transcript 1 (MULT-1)^[24]. In addition to membrane-bound NKG2DLs, secreted forms of the ligands have been also identified in humans.

NKG2DL are expressed on diseased or stressed cells, and numerous stress pathways induce their up-regulation, including viral and bacterial infection, cellular transformation, oxidative or genotoxic stress^[25]. A large body of evidence indicates that HBV infection modulates NKG2D-mediated immune responses. The engagement of NKG2D to its ligands is a sufficient stimulus to activate cytotoxicity and cytokine production by NK cells, to promote antitumor or antiviral immune responses and autoimmune diseases, to provide a co-stimulatory signal for the activation of CD8⁺ T cells and probably other T cells and contributes to apoptotic cell death^[18,21,22,26]. NKG2DL also participate in the cross-talk between immune cells, which can regulate innate and adaptive responses. Increased expression of NKG2DL induces NK cell-mediated cytotoxicity to eliminate over-stimulated macrophages^[27], while in response to Toll-like receptor stimulation NKG2DL expressed on myeloid cells are up-regulated, contributing to T cell and NK cell activation^[28].

NKG2D PATHWAY IN HBV INFECTION

There is increasing evidence that activation of the NKG2D-ligand pathway contributes to the outcome of HBV infection. Studies in a transgenic mouse model

of acute infection, demonstrated that the blockage of NKG2D receptor on only NK T cells prevents HBV infection by raising efficient acute immune responses and that the interaction between NKG2D and its RAET-1 ligand is essential in inducing HBV immunity^[18]. These findings suggest that in the early stages of infection, NK T cells may be activated first in an HBV-specific and NKG2D-dependent manner that may in turn lead to the activation of NK cells. Furthermore, early in HBV infection there is an overexpression of the soluble form of MICA (sMICA) in comparison to later stages of infection, leading to the internalization and degradation of NKG2D receptor and hence to defective NK and NK T activity^[26,29]. Other studies demonstrated that sMICA levels increase together with progression of liver disease^[30]. Consequently, the persistence of high sMICA levels from the early to later stages may result in the establishment of CHB infection and the initiation of liver cirrhosis and HCC.

In CHB infection, NKG2D expression on intrahepatic virus-specific CD8⁺ T cells is shown to be essential in the recognition of virus-infected hepatocytes through the up-regulation of IL-15^[31]. More specifically, increased NKG2D expression provides a co-stimulatory signal in TCR-mediated CD8⁺ T cell activation. Enhanced NKG2D and IL-15 expression may act in a way to lower the activation threshold of effector CD8⁺ T cells, and hence to allow the efficient recognition of hepatocytes that express low levels of viral antigens^[31]. In accordance with these findings, down-regulation of NKG2D and co-stimulatory receptor 2B4 on circulating NK cells has been associated with the impaired function of NK cells in CHB patients^[32]. On the other hand, hepatic NK cell-mediated killing through NKG2D recognition in CHB infection induces the development of liver fibrosis and hepatic damage. NKG2D activation through the overexpression of NKG2DL on the infected hepatocytes is shown to prime them to become a target for NK cell-mediated killing and to lead to the subsequent development of liver injury^[33]. In addition, in a transgenic mouse model, NK cell activation *via* the up-regulation of RAET-1 or MULT-1 on hepatocytes was shown to account for the oversensitive autoimmune hepatocyte injury, with NK T cells working as helpers necessary for NK cell activation^[34].

NKG2DL EXPRESSION IS INHIBITED IN HBV-INDUCED HCC

NK and T cell activity is repressed during HCC progression and NKG2D recognition of tumor cells is implicated in the process. MIC molecules are highly expressed in transformed cells and contribute in tumor immune surveillance by promoting antitumor NK and T cell responses^[35]. Tumor cells have also developed strategies to escape NKG2D immunity by the down-regulation of NKG2DL^[36]. Our unpublished data and

others demonstrated that HBV infection represses MICA expression in the liver of CHB patients and on hepatic tumor cell lines^[37,38]. Inhibition of viral replication in HBV-expressing HCC cells in transgenic mice is reported to restore MICA expression and to induce NK-cell mediated cytolysis^[38,39]. In addition, increased levels of sMICA released from the surface of tumor cells in CHB patients have been shown to sequester NKG2D in the cytoplasm and to inhibit cell-surface NKG2D expression and effector functions in malignant tumors^[19,30,40]. Therefore, a tumor-specific expression pattern of MICA exists in HBV-induced HCC, while NK cells recognize hepatoma cells *via* MICA-NKG2D interaction. The reduced MICA expression by HBV weakens the immune surveillance of NK cells in chronic infection while the overexpression of sMICA by HCC cells inhibits NKG2D function leading to the impairment of NK and T cells. The persistence of high sMICA levels at the late stages of CHB infection contributes to liver cirrhosis and HCC evasion^[30].

NKG2DL POLYMORPHISMS ASSOCIATE WITH HBV PERSISTENCE

NKG2DL are highly polymorphic, more than 70 alleles have been identified for the MICA gene and more than 30 alleles for the MICB gene^[24]. Interestingly, allelic variants of these ligands have been shown to bind to NKG2D receptor with different affinities resulting in different degrees of activation to promote NKG2D-mediated responses. Differential distribution of MICA alleles affects the outcome of HBV infection and HCC development. Homozygous genotype *MICA-175Ser/Ser*, allele *MICA-175Ser*, haplotypes, as well as the microsatellite polymorphisms associate with CHB infection^[29]. Among the MICA variants, *MICA*015* allele is characterized by high affinity to NKG2D and has been correlated with HBV persistence in a small cohort of patients^[41]. A non-synonymous substitution in exon 3 (*MICA-129Met/Val*) is known to play a distinct role in NKG2D binding: *MICA-129Met* is strong binder while *MICA-129Val* is a weak binder^[42]. The genotype *MICA-129Met/Met* and the allele *MICA-129Met* are reported to increase the risk of HBV-induced HCC^[29]. Notably, strong binding of the *MICA-129 Met* allele to NKG2D can induce the shedding of sMICA and subsequent NKG2D inhibition, resulting in impaired NK and T cell activity and promoting tumor evasion. However, alleles that contribute to lower sMICA levels are also risk factors for HCC occurrence. This could be explained by the fact that individuals with these risk alleles would also express low levels of membrane-bound MICA leading to a poor recognition of tumor cells^[43] or the shedding of sMICA may be influenced by these risk alleles during immune surveillance. Nevertheless, differential binding between NKG2D and the MICA protein as well as the MICA shedding process plays a pivotal role in tumor surveillance in HBV infection.

NKG2DLS POST-TRANSCRIPTIONAL REGULATION BY HBV

Numerous findings including our own observations show that different cells and tissues express mRNA for NKG2DL but may lack the expression of NKG2DL proteins, indicating that at least some NKG2DL are regulated post-transcriptionally. Indeed, a group of endogenous cellular microRNAs (miRNAs) have been identified that bind to the 3'-untranslated region (3'-UTR) of MICA and MICB and repress their translation^[44,45]. In addition, MICA and MICB expression is upregulated upon silencing of Dicer, a key protein in the miRNA processing pathway^[39]. HBV as well as HBsAg and HBx viral proteins are reported to deregulate a number of cellular miRNAs^[46,47]. HBsAg was shown to repress the expression of MICA and MICB in HCC cells by inducing 142 cellular miRNAs *via* targeting 3'-UTRs of their mRNAs and therefore enhancing the resistance of HCC cells to NKG2D-mediated cytotoxicity^[39]. This down-regulation was shown to be partially restored by inhibiting the activities of HBsAg-induced miRNAs^[39]. These findings suggest that HBsAg prevents NKG2D-mediated elimination of HCC cells by inducing cellular miRNAs to inhibit MIC expression.

CONCLUDING REMARKS

The NKG2D receptor plays an important role in the outcome of HBV infection but the exact mechanisms involved are still elusive. We know that the NKG2D-induced elimination of infected hepatocytes *via* NKG2DL upregulation can be both protective by inducing viral clearance *via* NK activation early in infection and harmful by leading to susceptibility to liver injury later in infection. A tumor-specific pattern of MICA expression exists in CHB infection. MICA proteins are expressed both as membrane-bound MICA and in soluble form and the shedding of MICA is crucial in NKG2D-mediated responses to tumor. HBV can induce tumor invasion by down-regulating MICA expression on the cell surface of tumor cells and hence weakening NK surveillance while the persistence of high sMICA levels from the early to later stages of chronic infection can result to the initiation of liver cirrhosis and HCC. The NKG2D-MICA interaction may serve as an efficient innate pathway of immune surveillance against HCC and tumor evasion in CHB infection.

NKG2DLs ligands are highly polymorphic. MICA allelic variants bind with variable affinity to NKG2D resulting in differential sMICA shedding and activation of NKG2D-mediated responses. A number of MICA polymorphisms have been identified to be risk factors in HBV-induced HCC occurrence. HBV and its viral products are shown to control the expression of NKG2DLs in HCC development by regulating cellular miRNAs. Since HBV replicates less in tumor tissues than in adjacent non-tumor tissue, it is possible that decreased MIC expression in HCC

tissues is the consequence of down-regulation of HBV-encoded proteins, such as HBsAg, which can control the expression of the cellular miRNAs. Post-transcriptional regulation of miRNAs has the advantage that NKG2DL are already transcribed and thus, upon infection, they can be rapidly expressed. In human cytomegalovirus (HCMV) infection, immediate-early proteins are able to display histone deacetylases, which induce the transcription of MICA and MICB mRNA^[48]. HBV is known to compromise host's epigenetic processes and particularly to induce the recruitment of histone deacetylases onto HBV covalently closed circular DNA minichromosome^[49]. Similar to HCMV, it is possible that HBV can influence NKG2DL expression post-transcriptionally by modulating the accumulation of histone deacetylases. A detailed characterization of the molecular players that link the HBV stimuli to the transcription of NKG2DL will be critical to advance our knowledge on how HBV circumvents the host's immunity. The manipulation of ligand expression shows many promises therapeutically. Understanding the mechanisms of NKG2D pathways will provide new insight on chronic HBV immunopathogenesis and HCC development and can lead to possibilities of developing effective treatment strategies.

REFERENCES

- 1 Cassidy A, Mossman S, Olivieri A, De Ridder M, Leroux-Roels G. Hepatitis B vaccine effectiveness in the face of global HBV genotype diversity. *Expert Rev Vaccines* 2011; **10**: 1709-1715 [PMID: 22085174 DOI: 10.1586/erv.11.151]
- 2 Lupberger J, Hildt E. Hepatitis B virus-induced oncogenesis. *World J Gastroenterol* 2007; **13**: 74-81 [PMID: 17206756 DOI: 10.3748/wjg.v13.i1.74]
- 3 Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; **379**: 1245-1255 [PMID: 22353262 DOI: 10.1016/S0140-6736(11)61347-0]
- 4 Fisicaro P, Valdatta C, Boni C, Massari M, Mori C, Zerbini A, Orlandini A, Sacchelli L, Missale G, Ferrari C. Early kinetics of innate and adaptive immune responses during hepatitis B virus infection. *Gut* 2009; **58**: 974-982 [PMID: 19201769]
- 5 Webster GJ, Reignat S, Maini MK, Whalley SA, Ogg GS, King A, Brown D, Amlot PL, Williams R, Vergani D, Dusheiko GM, Bertolotti A. Incubation phase of acute hepatitis B in man: dynamic of cellular immune mechanisms. *Hepatology* 2000; **32**: 1117-1124 [PMID: 11050064]
- 6 Zhao J, Li Y, Jin L, Zhang S, Fan R, Sun Y, Zhou C, Shang Q, Li W, Zhang Z, Wang FS. Natural killer cells are characterized by the concomitantly increased interferon- γ and cytotoxicity in acute resolved hepatitis B patients. *PLoS One* 2012; **7**: e49135 [PMID: 23133672 DOI: 10.1371/journal.pone.0049135]
- 7 Bertolotti A, Ferrari C. Kinetics of the immune response during HBV and HCV infection. *Hepatology* 2003; **38**: 4-13 [PMID: 12829979 DOI: 10.1053/jhep.2003.50310]
- 8 Guidotti LG, Rochford R, Chung J, Shapiro M, Purcell R, Chisari FV. Viral clearance without destruction of infected cells during acute HBV infection. *Science* 1999; **284**: 825-829 [PMID: 10221919 DOI: 10.1126/science.284.5415.825]
- 9 Kajino K, Jilbert AR, Saputelli J, Aldrich CE, Cullen J, Mason WS. Woodchuck hepatitis virus infections: very rapid recovery after a prolonged viremia and infection of virtually every hepatocyte. *J Virol* 1994; **68**: 5792-5803 [PMID: 7914548]
- 10 Li Y, Wang JJ, Gao S, Liu Q, Bai J, Zhao XQ, Hao YH, Ding HH, Zhu F, Yang DL, Zhao XP. Decreased peripheral natural killer cells activity in the immune activated stage of chronic hepatitis B. *PLoS*

- One* 2014; **9**: e86927 [PMID: 24520324 DOI: 10.1371/journal.pone.0086927]
- 11 **Oliviero B**, Varchetta S, Paudice E, Michelone G, Zaramella M, Mavilio D, De Filippi F, Bruno S, Mondelli MU. Natural killer cell functional dichotomy in chronic hepatitis B and chronic hepatitis C virus infections. *Gastroenterology* 2009; **137**: 1151-1160, 1160. e1-7 [PMID: 19470388 DOI: 10.1053/j.gastro.2009.05.047]
 - 12 **Sprengers D**, van der Molen RG, Kusters JG, Hansen B, Niesters HG, Schalm SW, Janssen HL. Different composition of intrahepatic lymphocytes in the immune-tolerance and immune-clearance phase of chronic hepatitis B. *J Med Virol* 2006; **78**: 561-568 [PMID: 16555293 DOI: 10.1002/jmv.20576]
 - 13 **Dunn C**, Brunetto M, Reynolds G, Christophides T, Kennedy PT, Lampertico P, Das A, Lopes AR, Borrow P, Williams K, Humphreys E, Afford S, Adams DH, Bertolotti A, Maini MK. Cytokines induced during chronic hepatitis B virus infection promote a pathway for NK cell-mediated liver damage. *J Exp Med* 2007; **204**: 667-680 [PMID: 17353365 DOI: 10.1084/jem.20061287]
 - 14 **Zou Z**, Xu D, Li B, Xin S, Zhang Z, Huang L, Fu J, Yang Y, Jin L, Zhao JM, Shi M, Zhou G, Sun Y, Wang FS. Compartmentalization and its implication for peripheral immunologically-competent cells to the liver in patients with HBV-related acute-on-chronic liver failure. *Hepatology* 2009; **39**: 1198-1207 [PMID: 19788691 DOI: 10.1111/j.1872-034X.2009.00571.x]
 - 15 **Bertolotti A**, Maini MK. Protection or damage: a dual role for the virus-specific cytotoxic T lymphocyte response in hepatitis B and C infection? *Curr Opin Microbiol* 2000; **3**: 387-392 [PMID: 10972499 DOI: 10.1016/S0952-7915(00)00108-4]
 - 16 **Peppas D**, Gill US, Reynolds G, Easom NJ, Pallett LJ, Schurich A, Micco L, Nebbia G, Singh HD, Adams DH, Kennedy PT, Maini MK. Up-regulation of a death receptor renders antiviral T cells susceptible to NK cell-mediated deletion. *J Exp Med* 2013; **210**: 99-114 [PMID: 23254287 DOI: 10.1084/jem.20121172]
 - 17 **Baron JL**, Gardiner L, Nishimura S, Shinkai K, Locksley R, Ganem D. Activation of a nonclassical NKT cell subset in a transgenic mouse model of hepatitis B virus infection. *Immunity* 2002; **16**: 583-594 [PMID: 11970881 DOI: 10.1016/S1074-7613(02)00305-9]
 - 18 **Vilarinho S**, Ogasawara K, Nishimura S, Lanier LL, Baron JL. Blockade of NKG2D on NKT cells prevents hepatitis and the acute immune response to hepatitis B virus. *Proc Natl Acad Sci USA* 2007; **104**: 18187-18192 [PMID: 17991774 DOI: 10.1073/pnas.0708968104]
 - 19 **Groh V**, Bruhl A, El-Gabalawy H, Nelson JL, Spies T. Stimulation of T cell autoreactivity by anomalous expression of NKG2D and its MIC ligands in rheumatoid arthritis. *Proc Natl Acad Sci USA* 2003; **100**: 9452-9457 [PMID: 12878725 DOI: 10.1073/pnas.1632807100]
 - 20 **Ogasawara K**, Hamerman JA, Ehrlich LR, Bour-Jordan H, Santamaria P, Bluestone JA, Lanier LL. NKG2D blockade prevents autoimmune diabetes in NOD mice. *Immunity* 2004; **20**: 757-767 [PMID: 15189740 DOI: 10.1016/j.immuni.2004.05.008]
 - 21 **Cerwenka A**, Bakker AB, McClanahan T, Wagner J, Wu J, Phillips JH, Lanier LL. Retinoic acid early inducible genes define a ligand family for the activating NKG2D receptor in mice. *Immunity* 2000; **12**: 721-727 [PMID: 10894171 DOI: 10.1016/S1074-7613(00)80222-8]
 - 22 **Wu J**, Groh V, Spies T. T cell antigen receptor engagement and specificity in the recognition of stress-inducible MHC class I-related chains by human epithelial gamma delta T cells. *J Immunol* 2002; **169**: 1236-1240 [PMID: 12133944]
 - 23 **Lanier LL**. NK cell recognition. *Annu Rev Immunol* 2005; **23**: 225-274 [PMID: 15771571]
 - 24 **Stern-Ginossar N**, Mandelboim O. An integrated view of the regulation of NKG2D ligands. *Immunology* 2009; **128**: 1-6 [PMID: 19689730 DOI: 10.1111/j.1365-2567.2009.03147.x]
 - 25 **Gasser S**, Orsulic S, Brown EJ, Raulet DH. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. *Nature* 2005; **436**: 1186-1190 [PMID: 15995699 DOI: 10.1038/nature03884]
 - 26 **Kahraman A**, Fingas CD, Syn WK, Gerken G, Canbay A. Role of stress-induced NKG2D ligands in liver diseases. *Liver Int* 2012; **32**: 370-382 [PMID: 22097967 DOI: 10.1111/j.1478-3231.2011.02608.x]
 - 27 **Nedvetzki S**, Sowinski S, Eagle RA, Harris J, Vély F, Pende D, Trowsdale J, Vivier E, Gordon S, Davis DM. Reciprocal regulation of human natural killer cells and macrophages associated with distinct immune synapses. *Blood* 2007; **109**: 3776-3785 [PMID: 17218381 DOI: 10.1182/blood-2006-10-052977]
 - 28 **Ebihara T**, Masuda H, Akazawa T, Shingai M, Kikuta H, Ariga T, Matsumoto M, Seya T. Induction of NKG2D ligands on human dendritic cells by TLR ligand stimulation and RNA virus infection. *Int Immunol* 2007; **19**: 1145-1155 [PMID: 17878262 DOI: 10.1093/intimm/dxm073]
 - 29 **Tong HV**, Toan NL, Song LH, Bock CT, Kremsner PG, Velavan TP. Hepatitis B virus-induced hepatocellular carcinoma: functional roles of MICA variants. *J Viral Hepat* 2013; **20**: 687-698 [PMID: 24010643 DOI: 10.1111/jvh.12089]
 - 30 **Jinushi M**, Takehara T, Tatsumi T, Hiramatsu N, Sakamori R, Yamaguchi S, Hayashi N. Impairment of natural killer cell and dendritic cell functions by the soluble form of MHC class I-related chain A in advanced human hepatocellular carcinomas. *J Hepatol* 2005; **43**: 1013-1020 [PMID: 16168521 DOI: 10.1016/j.jhep.2005.05.026]
 - 31 **Kennedy PT**, Gehring AJ, Nowbath A, Selden C, Quaglia A, Dhillon A, Dusheiko G, Bertolotti A. The expression and function of NKG2D molecule on intrahepatic CD8+ T cells in chronic viral hepatitis. *J Viral Hepat* 2008; **15**: 901-909 [PMID: 19087227 DOI: 10.1111/j.1365-2893.2008.01049.x]
 - 32 **Sun C**, Fu B, Gao Y, Liao X, Sun R, Tian Z, Wei H. TGF- β 1 down-regulation of NKG2D/DAP10 and 2B4/SAP expression on human NK cells contributes to HBV persistence. *PLoS Pathog* 2012; **8**: e1002594 [PMID: 22438812 DOI: 10.1371/journal.ppat.1002594]
 - 33 **Radaeva S**, Sun R, Jaruga B, Nguyen VT, Tian Z, Gao B. Natural killer cells ameliorate liver fibrosis by killing activated stellate cells in NKG2D-dependent and tumor necrosis factor-related apoptosis-inducing ligand-dependent manners. *Gastroenterology* 2006; **130**: 435-452 [PMID: 16472598 DOI: 10.1053/j.gastro.2005.10.055]
 - 34 **Chen Y**, Wei H, Sun R, Dong Z, Zhang J, Tian Z. Increased susceptibility to liver injury in hepatitis B virus transgenic mice involves NKG2D-ligand interaction and natural killer cells. *Hepatology* 2007; **46**: 706-715 [PMID: 17626270 DOI: 10.1002/hep.21872]
 - 35 **Groh V**, Rhinehart R, Secrist H, Bauer S, Grabstein KH, Spies T. Broad tumor-associated expression and recognition by tumor-derived gamma delta T cells of MICA and MICB. *Proc Natl Acad Sci USA* 1999; **96**: 6879-6884 [PMID: 10359807 DOI: 10.1073/pnas.96.12.6879]
 - 36 **Sène D**, Levasseur F, Abel M, Lambert M, Camous X, Hernandez C, Pène V, Rosenberg AR, Jouvin-Marche E, Marche PN, Cacoub P, Caillat-Zucman S. Hepatitis C virus (HCV) evades NKG2D-dependent NK cell responses through NNSA-mediated imbalance of inflammatory cytokines. *PLoS Pathog* 2010; **6**: e1001184 [PMID: 21085608 DOI: 10.1371/journal.ppat.1001184]
 - 37 **Chen CJ**, Yang HI, Su J, Jen CL, You SL, Lu SN, Huang GT, Iloeje UH. Risk of hepatocellular carcinoma across a biological gradient of serum hepatitis B virus DNA level. *JAMA* 2006; **295**: 65-73 [PMID: 16391218 DOI: 10.1001/jama.295.1.65]
 - 38 **Tang KF**, Chen M, Xie J, Song GB, Shi YS, Liu Q, Mei ZC, Steinle A, Ren H. Inhibition of hepatitis B virus replication by small interference RNA induces expression of MICA in HepG2.2.15 cells. *Med Microbiol Immunol* 2009; **198**: 27-32 [PMID: 18685862 DOI: 10.1007/s00430-008-0101-6]
 - 39 **Wu J**, Zhang XJ, Shi KQ, Chen YP, Ren YF, Song YJ, Li G, Xue YF, Fang YX, Deng ZJ, Xu X, Gao J, Tang KF. Hepatitis B surface antigen inhibits MICA and MICB expression via induction of cellular miRNAs in hepatocellular carcinoma cells. *Carcinogenesis* 2014; **35**: 155-163 [PMID: 23917076 DOI: 10.1093/carcin/bgt268]
 - 40 **Dobrovina ES**, Dobrovina MM, Vider E, Sisson RB, O'Reilly RJ, Dupont B, Vyas YM. Evasion from NK cell immunity by MHC class I chain-related molecules expressing colon adenocarcinoma. *J Immunol* 2003; **171**: 6891-6899 [PMID: 14662896]
 - 41 **Karacki PS**, Gao X, Thio CL, Thomas DL, Goedert JJ, Vlahov D,

- Kaslow RA, Strathdee S, Hilgartner MW, O'Brien SJ, Carrington M. MICA and recovery from hepatitis C virus and hepatitis B virus infections. *Genes Immun* 2004; **5**: 261-266 [PMID: 15029237 DOI: 10.1038/sj.gene.6364065]
- 42 **Steinle A**, Li P, Morris DL, Groh V, Lanier LL, Strong RK, Spies T. Interactions of human NKG2D with its ligands MICA, MICB, and homologs of the mouse RAE-1 protein family. *Immunogenetics* 2001; **53**: 279-287 [PMID: 11491531 DOI: 10.1007/s002510100325]
- 43 **Kumar V**, Kato N, Urabe Y, Takahashi A, Muroyama R, Hosono N, Otsuka M, Tateishi R, Omata M, Nakagawa H, Koike K, Kamatani N, Kubo M, Nakamura Y, Matsuda K. Genome-wide association study identifies a susceptibility locus for HCV-induced hepatocellular carcinoma. *Nat Genet* 2011; **43**: 455-458 [PMID: 21499248 DOI: 10.1038/ng.809]
- 44 **Stern-Ginossar N**, Gur C, Biton M, Horwitz E, Elboim M, Stanietsky N, Mandelboim M, Mandelboim O. Human microRNAs regulate stress-induced immune responses mediated by the receptor NKG2D. *Nat Immunol* 2008; **9**: 1065-1073 [PMID: 18677316 DOI: 10.1038/ni.1642]
- 45 **Yadav D**, Ngolab J, Lim RS, Krishnamurthy S, Bui JD. Cutting edge: down-regulation of MHC class I-related chain A on tumor cells by IFN-gamma-induced microRNA. *J Immunol* 2009; **182**: 39-43 [PMID: 19109132]
- 46 **Kong G**, Zhang J, Zhang S, Shan C, Ye L, Zhang X. Upregulated microRNA-29a by hepatitis B virus X protein enhances hepatoma cell migration by targeting PTEN in cell culture model. *PLoS One* 2011; **6**: e19518 [PMID: 21573166]
- 47 **Ura S**, Honda M, Yamashita T, Ueda T, Takatori H, Nishino R, Sunakozaka H, Sakai Y, Horimoto K, Kaneko S. Differential microRNA expression between hepatitis B and hepatitis C leading disease progression to hepatocellular carcinoma. *Hepatology* 2009; **49**: 1098-1112 [PMID: 19173277]
- 48 **van Zonneveld M**, Zondervan PE, Cakaloglu Y, Simon C, Akarca US, So TM, Flink HJ, de Man RA, Schalm SW, Janssen HL. Peg-interferon improves liver histology in patients with HBeAg-positive chronic hepatitis B: no additional benefit of combination with lamivudine. *Liver Int* 2006; **26**: 399-405 [PMID: 16629642]
- 49 **Pollicino T**, Belloni L, Raffa G, Pediconi N, Squadrito G, Raimondo G, Levrero M. Hepatitis B virus replication is regulated by the acetylation status of hepatitis B virus cccDNA-bound H3 and H4 histones. *Gastroenterology* 2006; **130**: 823-837 [PMID: 16530522]

P- Reviewer: Canbay AE, Sener A, Yu ML **S- Editor:** Ji FF
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