MINIREVIEWS

Dendritic cells in hepatitis C virus infection: Key players in the *IFNL3*-genotype response

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Abstract

Recently, single nucleotide polymorphisms, in the vicinity of the interferon lambda 3 (*IFNL3*) gene have been identified as the strongest predictor of spontaneous and treatment induced clearance of hepatitis C virus (HCV) infection. Since then, increasing evidence has implicated the innate immune response in mediating the *IFNL3* genotype effect. Dendritic cells (DCs) are key to the host immune response in HCV infection and their vital role in the *IFNL3* genotype effect is emerging. Reports have identified subclasses of DCs, particularly myeloid DC2s and potentially plasmacytoid DCs as the major producers of IFNL3 in the setting of HCV infection. Given the complexities of dendritic cell biology and the conflicting current available data, this review aims to summarize what is currently known regarding the role of dendritic cells in HCV infection and to place it into context of what is know about lambda interferons and dendritic cells in general.

Core tip: Increasing evidence implicates the innate immune response in mediating the interferon lambda 3 (*IFNL3*) genotype effect in hepatitis C virus (HCV) infection. Dendritic cells (DCs) are essential players in the host immune response to HCV infection, especially with respect to the *IFNL3* genotype effect. Subsets of DCs, myeloid DC2s and potentially plasmacytoid DCs, appear to particularly important in orchestrating the *IFNL3* genotype effect.

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INTRODUCTION

An estimated 3% of the world's population is infected with hepatitis C virus (HCV)[1]. With low spontaneous clearance rates, 80% of individuals go on to develop chronic infection, which is associated with long term complications including cirrhosis, hepatocellular carcinoma and death from chronic liver failure[2]. Recently, single nucleotide polymorphisms (SNPs) in the region of the interferon lambda 3 (*IFNL3*; formerly known as *IL28B*) gene were identified to strongly predict spontaneous and treatment-induced clearance of HCV of

HCV infection[3-7]. *IFNL3* encodes IFNL3 a member of the type Ⅲ interferon (IFN) family and thus belongs to the group of innate immune cytokines. Dendritic cells (DC) are recognized as the major producers of IFNs and central players in the host immune response against HCV[8]. In this review we explore the role of DC in chronic hepatitis C (CHC) in the context of IFNL3 and its polymorphism.

IFNL3 POLYMORPHISMS IN HCV INFECTION

The poor treatment response rates, high economic burden and significant adverse effects associated with traditional antiviral therapy for CHC consisting of pegylated IFN-alpha and ribavirin (Peg-IFNα/RBV) motivated research into host genetic factors associated with successful HCV clearance. In 2009, four landmark genome wide association studies (GWAS) independently described SNPs in the vicinity of *IFNL3* that were dramatically predictive of response to Peg-IFNα/RBV therapy in patients with genotype 1 HCV[3-5,9]. The favourable variants of the two most widely studied SNPs, *rs12979860* and *rs8099917*, are the strongest pre-treatment predictors of SVR in genotype 1 HCV infection, but clearly also affect treatment response to Peg-IFNα/RBV in HCV genotype 2 and 3 infections[10]. Subsequently, this genetic variation has also been associated with spontaneous clearance of HCV[6,7] and liver inflammation in chronic HCV infection[11-13], strongly implicating the innate immune response in the *IFNL3* genetic response.

LAMBDA INTERFERONS

Three classes of IFNs are now recognized (type Ⅰ, Ⅱ and Ⅲ) and these cytokines are crucial to the establishment of an antiviral immune response. They are classified based on differences in structure, receptor and biological function: Type I IFNs include IFNA and IFN-beta (IFN-β), whereas the only type Ⅱ IFN is IFN-gamma (IFN-γ)[14]. The type Ⅲ or lambda IFNs were more recently identified in 2003 by two independent research groups[15,16]. Initially three members in this family were described: IFNL1 or IL29, IFNL2 or IL28A and IFNL3 or IL28B. Interestingly, lambda IFNL share similarities with both the IL10 family of cytokines and type I IFNs[17]. They signal through the same janus tyrosine kinase (JAK)/signal transducers and activators of transcription (STAT) pathway leading to induction of interferon-stimulated genes (ISGs) and antiviral activity[15,18]. Signaling through common pathways facilitates type Ⅰ and type Ⅲ IFNs to induce similar biological activities, mediated by the induction of nearly identical sets of more than 300 ISGs[19]. Lambda IFN induced antiviral activity has been reported against many different viruses including inhibition of HCV replication *in vitro*[19,20]; IFNL3 has been shown to inhibit HCV replication in three independent HCV models by the JAK/STAT pathway[21]. There is also *in vitro*

evidence that IFNA induces expression of IFNL genes and that both cytokines appear to enhance the activity of the other[22].

In addition to their antiviral properties, lambda IFNLs exert complex and varied effects on immune cell function that are likely context dependent: Briefly, lambda IFNs have been shown to reduce the production of T helper 2 (Th2) cytokines (IL-4, IL-13, IL-14 and IL-15) thus potentially favouring Th1 driven immune response[23,24]. Further, enhanced adaptive immunity has been suggested by IFNL3 induced reduction in regulatory T cells, increased CD8+ T cell numbers[25] and augmentation of CD8+ T cell cytotoxicity[26].

In 2013, a new polymorphism (*rs368234815*) located between the genes for *IFNL2* and *IFNL3* (Figure 1) was identified and found to induce a frame shift mutation resulting in transient expression of an IFN analogue, IFN-lamda 4 (*IFNL4*), in stimulated human hepatocytes[27]. The authors postulated that the genotype dependent production of the protein IFNL4 resulted in altered ISG expression and thus may explain the effects on viral clearance. *rs368234815* is in high linkage disequilibrium with *rs12979860*, but more strongly associated with spontaneous and treatment induced HCV clearance, especially in individuals of African ancestry. The exact mechanisms molecular functions of IFNL4 remain to be clarified[28,29].

INTERFERON LAMBDA RECEPTOR AND SIGNALING

All IFNLs signal through the same heterodimeric receptor complex. This is composed of a unique interferon lambda receptor 1 (IFNLR1) [also known as IL28R alpha or cytokine receptor family 2 member 12 (CRF2-12)] component and IL10R2[15,16]. Both subunits are required for signalling. IL10R2 is ubiquitously expressed while IFNLR1 displays restricted tissue expression, predominately on cells of epithelial origin (including: keratinocytes and cells of kidney, lung and gastrointestinal tract origin) as well as specific subsets of immune cells[30-32]. The *IFNLR1* gene generates several splice variants including: a full length, membrane bound IFNLR1 and secreted, soluble IFNLR1 protein[33].

Expression of *IFNLR1* mRNA in human immune cells, especially B, T and NK-cells, has been previously demonstrated[30]. However, these immune cells were shown to express relatively more soluble receptor, which is postulated to act as an inhibitor to IFNL activity[30]. In contrast to these reports high levels of IFNLR1 have been detected on plasmacytoid dendritic cells (pDCs) relative to other cell populations in peripheral blood mononuclear cells (PBMCs) by us and others[30,34,35]. Furthermore, we have demonstrated significant up-regulation of *IFNLR1* expression after IFNA stimulation in pDCs suggesting that IFNA may enhance IFNL receptor expression and sensitivity to IFNL. Analysis of the ratio of membrane-bound receptor (*IFNLR1*-mem) to soluble isoforms (*IFNLR1*-sol) for pDCs, demonstrated that the majority
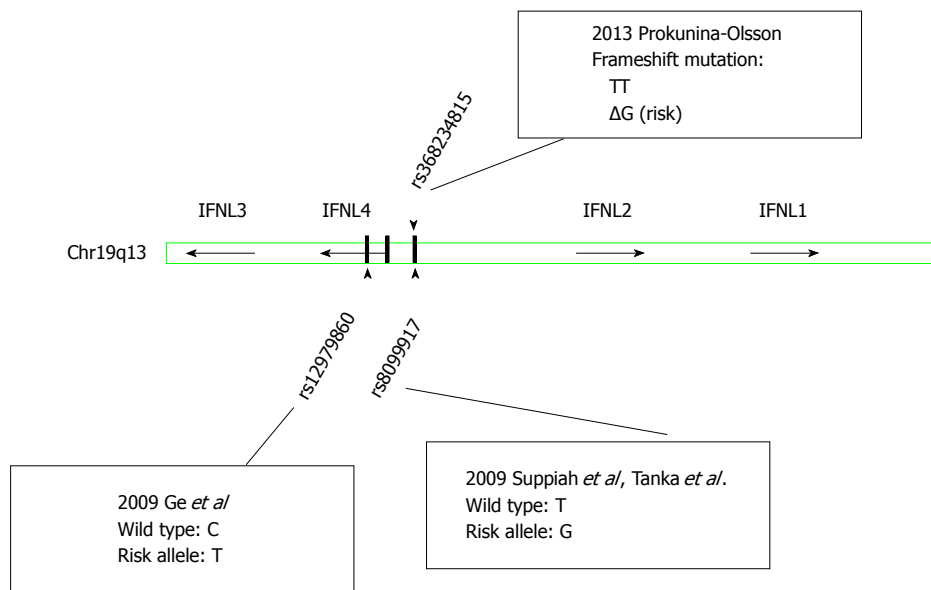
Figure 1 Schematic representation of single nucleotide polymorphisms idenditied in the interferon lambda gene locus. IFNL: Interferon lambda.

was the isoform encoding the membrane-associated or functional form of IFNLR1[36]. We have also demonstrated that *IFNLR1* expression was not significantly higher in HCV-infected liver biopsies compared with unstimulated pDCs[36].

Previous work has produced conflicting evidence on whether or not immune cells are a target for Type Ⅲ IFNs. Several studies have failed to show a response to IFN-lambdas (IFNL1 and/or IFNL2) by a variety of immune cells including B, T and natural killer cells (NK cells) as well as monocytes[30,37]. In contrast, several other human studies have revealed a direct effect of IFNLs on monocytes[38,39], dendritic cells[37] and T cells[23,38,40]. Work in pDCs has shown that IFNL1 results in altered expression of costimulatory molecules such as CD80[41]. We and others have demonstrated that pDCs are responsive to IFNL3 as detected by up-regulation of the ISG *MxA*[36] and increased production of IFNα[42]. IFNL may indeed act as an autocrine signal for pDCs with the ability to improve survival and enhance antiviral response[35]. This suggests a positive feedback loop for the production of IFNL3, particularly by DCs within HCV infected livers and the potential for an augmented response with IFNA therapy.

DENDRITIC CELLS

DCs are professional antigen presenting cells and play a major role in orchestrating the innate immune response against hepatitis C virus[43]. They are a rare cell population representing 0.3%-0.5% of normal human peripheral blood mononuclear cells[44,45]. They can be broadly categorized into two major subsets: pDCs and conventional myeloid DCs (mDCs). pDC and mDc differ significantly in terms of their morphology, phenotype and function; their individual features are summarized in Table 1.

mDCs originate from myeloid precursors in the bone marrow and display classic DC morphology with branched protrusions or dendrites[46]. mDCs are classical antigen presenting cells and have the ability to activate naive and effector T cells[43]. mDC can be further subdivided into mDC1 CD1c^{+} (blood antigen 1^{+}; BDCA1^{+}) or mDC2 CD141^{+} (blood antigen 3^{+}; BDCA3^{+})[47]. Human mDC2s are reported to be a counterpart of murine CD8a^{+} DC[48]. mDCs express a variety of toll like receptors (TLRs) such as TLR2 recognizing viral ligands (including HCV core and NS3) and TLR3 recognizing double stranded RNA viruses[49]. mDC2s express higher levels of TLR3 than mDC1s and lack TLR4 expression. mDC2s are the rarest DC population in bone marrow and peripheral blood[50]. mDC1s are the most potent producers of IL-12 thus rendering them more efficient than mDC2s at promoting cytotoxic CD8^{+} T-cell responses[51].

In contrast, pDC display a plasma cell morphology and under steady state conditions express lower levels of MHC class I, MHC class Ⅱ and co-stimulatory molecules such as CD86[8]. pDCs strongly express the pattern recognition receptors, TLR7 and TLR9, but not TLR3 and are thus capable of recognizing single stranded RNA and unmethlyated CpG-containing DNA ligands respectively[52]. Upon exposure to viral stimuli they are well recognized to produce massive amounts of type I interferons and acquire the capacity to present antigen[53]. In addition, they provide help to natural killer cells[54], regulate cell trafficking through the production of chemokines[55] and alter Th1/Th2 responses[56].

In CHC numbers of circulating pDCs and mDCs are reduced in peripheral blood compared with healthy controls[57-61] but both populations of DCs are significantly increased in the livers of CHC patients[61,62]. Furthermore in CHC, circulating numbers of DCs are inversely correlated with the serum alanine aminotransferase levels and severity of liver disease[63]. This suggests that immune cell trafficking to the liver may be the reason for reduced pe-

Table 1 Subsets of human dendritic cells			
	Plasmacytoid dendritic cells	Myeloid dendritic cells	
Morphology	Round, resemble plasma cells	Prominent cytoplasmic protrusions	
Phenotype	CD11C CD1a^{+}	CD11c^{+} CD1a^{+}	
	CD123^{high}	CD123^{low}	
		mDC1	mDC2
	BDCA-4^{+} (CD304^{+})		
	BDCA-2^{+} (CLEC4C)	BDCA-1^{+} (CD1c^{+})	BDCA-3^{+} (CD141^{+})
			CLEC9A
TLR receptor expression	TLR1, TLR6, TLR7, TLR9, TLR10	TLR1, TLR2, TLR3, TLR4, TLR5, TLR6, TLR7, TLR8,TLR10	TLR1, TLR2, TLR3,TLR6, TLR8, TLR10
MHC I	+	++	++
MHC II	+	+++	++
CD86	+	+++	++
CD40	+	++	+++
CXCR3	+++	+	++
ICOS L	++	+	+++

mDC: Myeloid dendritic cell; BDCA: Blood dendritic cell antigen; TLR: Toll like receptor; MHC: Major histocompatibility complex; CXCR3: Chemokine receptor 3; ICOSL: Inducible costimulator ligand.

ripheral DCs numbers. Enriched mDC2 numbers in CHC infected livers have also recently been demonstrated[42,64]. Apart from enrichment in the liver, hepatic mDC2s display higher expression of CD40, CD80, CD83 and CD86 than those seen in the circulating peripheral blood compartment suggesting a more mature phenotype[65].

DCS AND HOST IMMUNE RESPONSE TO HEPATITIS C VIRUS

Both the innate and adaptive arms of the immune system contribute to the host's ability to resolve HCV infection. The first line of defense against viral infections is the innate immune response with the IFNs playing a key role in induction of the antiviral state and control of HCV replication[66]. Specific viral motifs known as pathogen-associated molecular patterns are recognized by pattern recognition receptors (PRRs). Two groups of PRRs sense viral infection, RIG-I like-receptors and TLRs (TLR3, 7, 8 or 9)[67]. Downstream signalling leads to translocation of IFN regulatory factor 3 and synthesis of IFNs and pro-inflammatory cytokines[68].

Human pDCs recognize HCV predominantly through a TLR7 medicated pathway[59]. mDCs recognize HCV infection and mediate IFNL induction by the dsRNA sensing, TLR3-mediatd pathway[42]. Subsequently secreted IFNs bind to the IFN receptors and activate the JAK/STAT pathway leading to the induction of ISGs[69]. The expression of ISGs establishes an antiviral state including in neighboring uninfected hepatocytes. However, the induction of the endogenous IFN system in the liver has limited antiviral efficiency with, persistence of HCV observed for decades despite the expression of hundreds of ISGs[70,71] In fact, it is now well established that patients with an activated endogenous IFN system are poor responders to IFNA based therapies[70-72]. Interestingly, there is evidence that hepatic IFNL rather than type I IFN induction is more closely correlated with the strength of the ISG response[73].

HCV has the ability to impede the IFN response at several levels including: NS3/4A protein cleaving adapter molecules and blocking PRR signalling; HCV core protein interfering with JAK/STAT signalling and ISG expression; NS5A inhibiting the function of several ISGs and HCV may interact directly with pDC to impair IFN production and promote apoptosis[74]. In this context, HCV has the ability to evade the host antiviral response in hepatocytes through cleavage of key molecules involved in RIG-I and TLR3 signalling hence, interfering with the induction of endogenous IFNs and ISGs. pDC by contrast have the ability to overcome this evasion through direct cell contact and transfer of viral RNA from hepatocytes recognized by TLR7. This leads to the synthesis of interferon stimulated genes and secretion of IFNs[59]. There is some evidence that in CHC infection DC function is impaired as a result of reduced antigen presentation to CD4^{+} T cells mediated through interference by HCV proteins[43].

DENDRITIC CELLS ARE THE MAJOR PRODUCERS OF INTERFERON LAMBDA

There is evidence that human hepatocytes, DCs and macrophages all produce IFNL in response to HCV infection[41,75-79]. Importantly, mDC2 peripheral blood DCs have been identified by several groups as major producers of IFNL in HCV infection[42,65]. Data suggests that IFNL induction is dependent on direct cell to cell interaction with HCV infected hepatoma cells mediated through TLR3 signalling[42]. In comparison to other DC subsets mDC2s produced large amounts of IFNL when stimulated with cell-cultured HCV and HCV-transfected Huh7.5.1 cells[65]. This is further supported by evidence that the mouse homologue for human mDC2, CD8 alpha^{+} cells, are potent producers of IFNL2 and IFNL3 following TLR3 activation[80].
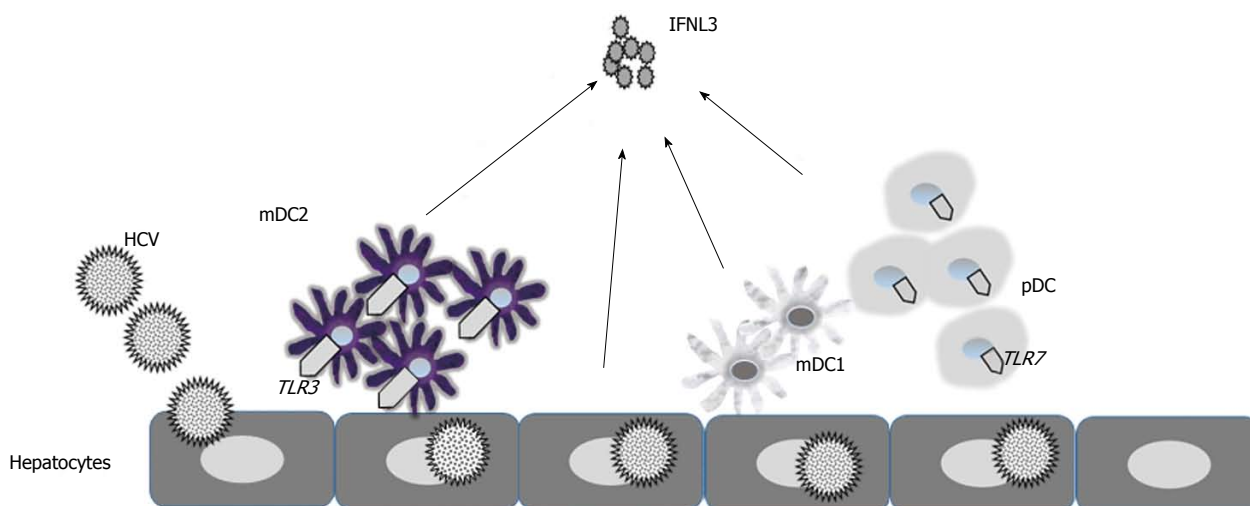
Figure 2 Schematic representation of interferon lambda 3 production in hepatitis C virus infection. Dendritic cell populations are enhanced in hepatitis C virus (HCV) infected livers. In response to HCV infection hepatocytes and dendritics produce interferon lambda (IFNL). However, recent reports suggest myeloid dendritic cell 2 (mDC2) are the major producers of IFNL3. IFNL3 production is mediated *via* toll like receptor (TLR)3 in mDC2 and TLR7 in plasmacytoid dendritic cell (pDC).

In contrast to these studies Murata *et al*[81] found that mDC2s stimulated by TLR3 agonists and pDCs stimulated by TLR7 agonists both produce large amounts of IFNL3. Importantly, detectable levels of IFNL3 were only demonstrated by TLR7 agonists and not TLR3 agonists in PBMCs. There was evidence of a more robust production of *IFNL3* mRNA in PBMC of patients with hepatitis C with the favorable *IFNL3* genotype (*rs8099917* TT) after stimulation with TLR7 agonists[81]. Importantly, this study detected that induction of IFNL3 protein was strongly correlated with Peg-IFNα/RBV treatment response in CHC[81] and that this measurement was a more accurate predictor of treatment response (95.7%) than *IFNL3* genotyping (65.2%)[81] (Figure 2).

To date, the literature has been conflicting as to whether *IFNL3* genotype alters *IFNL3* expression. Early work suggested higher expression in whole blood in the responder genotype[4,5]. However, similar studies in PBMCs did not confirm this association[3,42]. In several independent reports examining liver biopsies from subjects with CHC, no association between *IFNL3* expression and *IFNL3* genotype was noted[82-84]. Yoshio *et al*[65] identified greater IFNL3 production by mDC2s of patients with *IFNL3* responder genotypes *in vitro* with HCV co-culture but not TLR3 agonists. Other reports have found no *IFNL3* genotype association with IFNL production in mDC2s[42] or pDCs[36]. Thus, it is possible that IFNL3 production is temporally regulated, cell type and context dependent and that genotype differences may only be observed in particular cell populations at crucial stages of infection. Further complicating DC analysis is evidence that peripheral blood DC differ from tissue resident DC[85,86].

CONCLUSION

Since the identification *IFNL3* polymorphisms as important predictors of HCV clearance in 2009, signficant progress has been made relating to the underlying mecha-

nisms: Particularly, dendritic cell subsets such as mDC2s and potentially pDCs seem to be important to IFNL3 phenomena. Given their pivotal roles in innate and adaptive immunity, genetically determined, differential regulation of IFNL3 expression is thus likely to control disease outcomes. It has remained difficult, however, to pinpoint exactly, how the polymorphism translates into different regulation. Further research is required to clarify the genetic association with clinical outcomes and how IFNL3 medicated DC responses change the ultimate outcome of HCV infection.

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