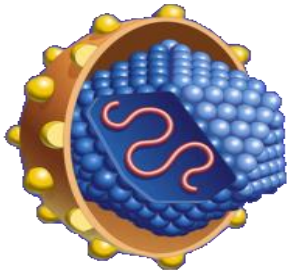
“Pathogenesis of HCV-related lymphoproliferative disorders”

Laura Gragnani

MASVE

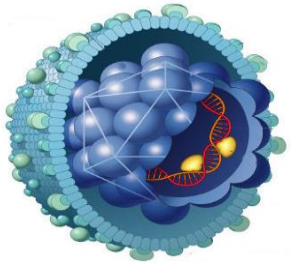
HBV & HCV- different features

HCV



- CHRONIC IN 85% OF THOSE INFECTED
- NO VACCINE AVAILABLE
- GENOME: RNA
- SEXUAL TRANSMISSION: VERY LOW RATE
- COMPLETELY ERADICABLE BY THERAPY

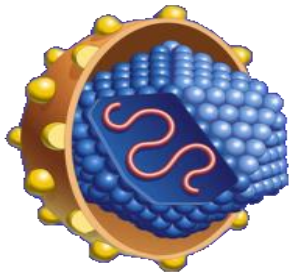
HBV

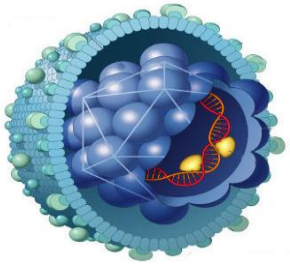


- CHRONIC CARRIER STATE IN 6% OF INFECTED
- VACCINE AVAILABLE
- GENOME: DNA
- SEXUALLY TRANSMITTED
- NOT COMPLETELY ERADICABLE (INTEGRATION)

HBV & HCV- similarities

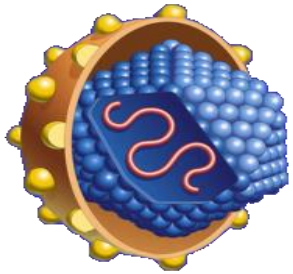
HCV & HBV





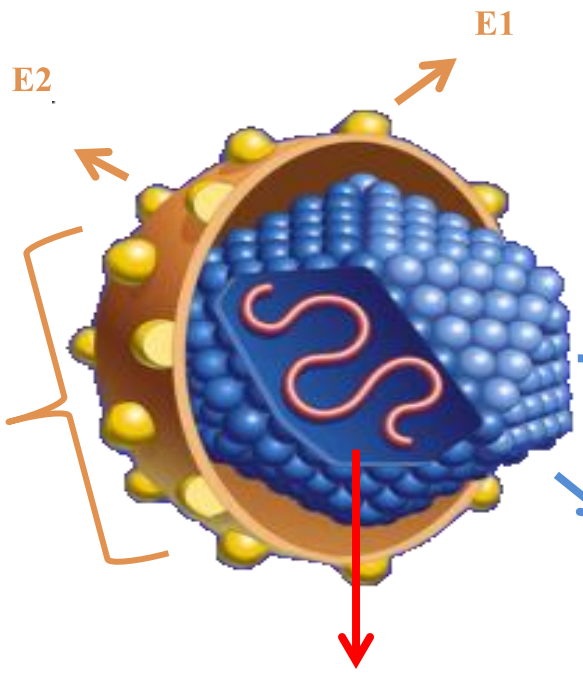
- SAME HIGH TROPISM FOR LIVER CELLS (HEPATOCYTES)
- SIMILAR NATURAL HISTORY IN TERMS OF LIVER DAMAGE DURING CHRONIC INFECTION
- BOTH CAN CAUSE HEPATOCELLULAR CARCINOMA (HCC), THE MOST DIFFUSED LIVER CANCER

HCV- general features



- MAINLY TRANSMITTED VIA BLOOD (TRANSFUSIONS, INTRAVENOUS DRUG USE, USE OF CONTAMINATED TOOLS, ETC…)
- THE GENOME IS A SINGLE STRAND-RNA
- 6 DIFFERENT GENOTYPES ARE DESCRIBED (WITH A DIFFERENT SENSIBILITY TO DRUGS)

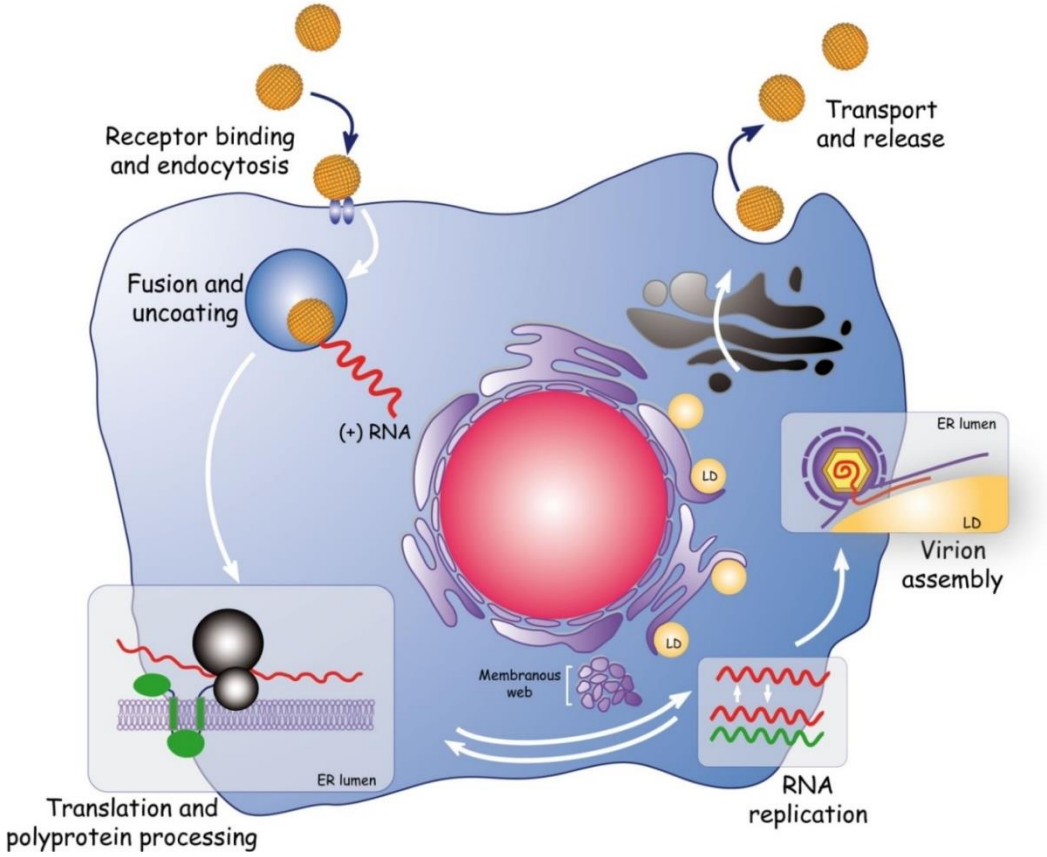
HCV structure



VIRAL ENVELOPE

(LIPIDS &GLYCOPROTEINS)

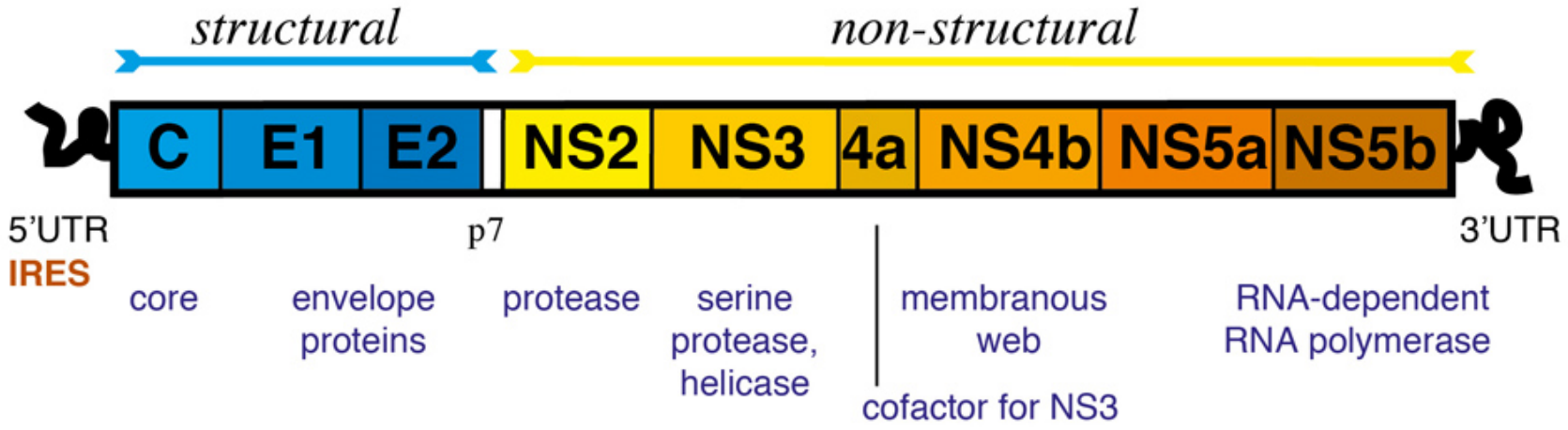
HCV life cycle



HCV genome

positive-strand RNA virus

9600 nucleotides - 3011 amino acids



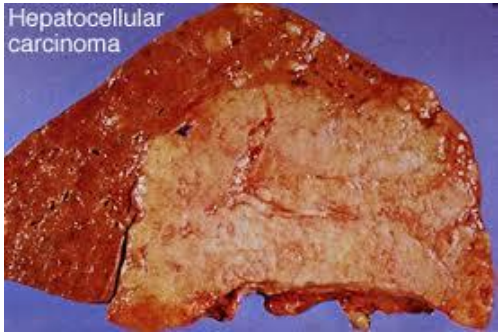
Progression of liver damage

PROGRESSION OF LIVER DAMAGE

HEALTHY LIVER	FIBROTIC LIVER	CIRRHOTIC LIVER	LIVER CANCER
			
A healthy liver is able to perform its normal functions effectively, e.g. aiding digestion and breaking down harmful drugs and poisons.	Continuous inflammation of the liver caused by hepatitis C can lead to fibrosis – the formation of scar tissue within the liver.	Extensive scarring can block the flow of blood through the liver and cause liver function to deteriorate over time - this is called cirrhosis.	Hepatitis C is a leading cause of liver cancer – the formation of a malignant tumour in the liver.

Hepatocellular carcinoma (HCC)

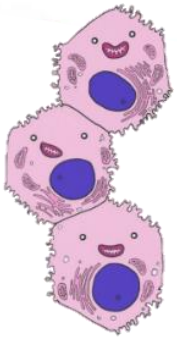
- Worldwide, HCC is the 5th most common cancer and the 3rd cause of death for cancer.
- HCC generally has a fulminant course, poor response to treatment, low resectability rate, high recurrence after resection/transplantation, poor prognosis.
- More than 70% of HCCs have a viral etiology
- The great majority of HCC develops on liver cirrhosis



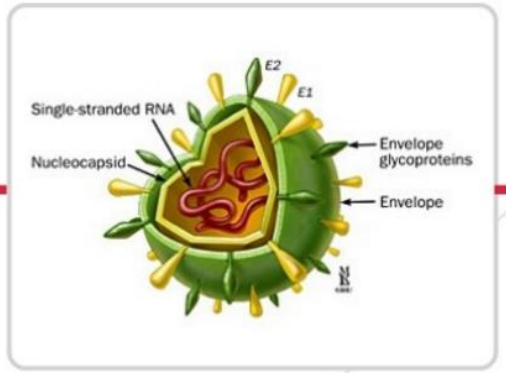
HCV chronic infection: more than one target cell

Hepatocyte

Choo. Science 1989



- Hepatitis
- Cirrhosis
- Hepatocarcinoma



Lymphocyte

Zignego. J Hepatol 1992
Ferri. Blood 1993

- Cryoglobulinemia
- Auto-Ab
- B-NHL

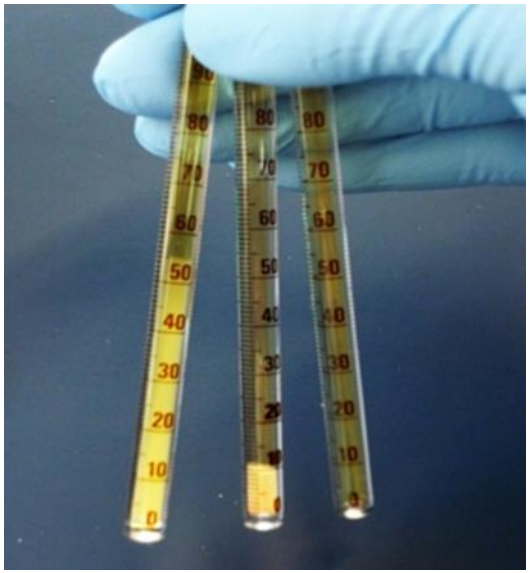
Courtesy of Patrice Cacoub; modified

Mixed Cryoglobulinemia - MC

- MC is a benign B-cell Lymphoproliferative Disorder (LPD) characterized by circulating Immune complexes **called cryoglobulins (CGs).**

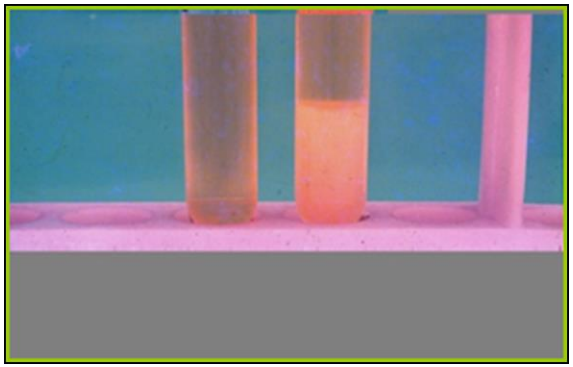
- **The CGs** include a **monoclonal (Type II) or polyclonal (Type III) IgM** and polyclonal IgGs.

- The IgM, with Rheumatoid Factor (RF) activity, is an autoantibody: that's why the MC is an autoimmune disorder too.



Mixed Cryoglobulinemia - MC

The cryoglobulins are so called because they precipitate in the blood serum when the temperature goes below 37° C



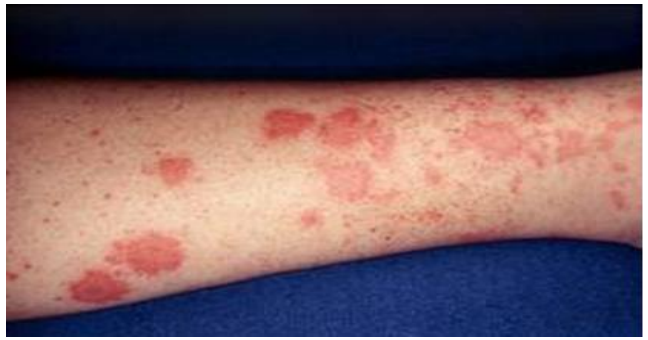
Strong association between HCV and MC (70-90%).

In Italy: MC-HCV+ >95%

Cryoglobulinemic Vasculitis - CV

Is the consequence of a systemic vasculitis (arterioles, capillaries, venules)

- Skin/Diffuse Vasculitis
- Joints
- MPG-nephritis
- Peripheral Neuropathy
- Lung alveolitis
- Endocrine disorders
- …



Eradication of viral infection generally coincide with the resolution of the MC syndrome, so the first-line therapeutic option is considered the antiviral treatment.

Pietrogrande et al. Autoimmun Rev. 2011

Cryoglobulinemic Vasculitis - CV

Why is cryo-vasculitis a so important and interesting model to study?

CV IS A CLINICALLY BENIGN BUT PRELYMPHOMATOUS CONDITION:

The overall risk of NHL in HCV-infected patients with symptomatic MC is greatly increased compared to the general population (up to 35 times in an Italian multicenter study).

Monti et al. Arch Intern Med. 2005

HCV chronic infection & lymphoma

- ✓ In 1994, a high prevalence of HCV infection in Italian patients with lymphoma was first reported in a limited cohort of patients

- ✓ In the last two decades, several pieces of evidence proved the association between HCV infection (with or without MC) and the occurrence of hematologic malignancies, mostly B-NHL

- ✓ A clear gradient of HCV-related lymphoma from North to South was also shown as for HCV infection

- ✓ Dedicated meta-analyses were able to confirm (although with different degrees), an increased risk of lymphoma in HCV infected subjects

Ferri C. et al, 1994; Zuckerman E. et al, 1997; de Sanjose S. et al, 2008; Hausfater P. et al, 2001; Gisbert P et al, Gastroenterology, 2003; Matsuo K et al, 2004; Negri E. et al, 2004; Dal Maso L. et al, 2006

HCV chronic infection & lymphoma

Table 1 Infections associated with non-Hodgkin lymphoma

Infectious agent	Lymphoma subtype
Lymphocyte-transforming viruses	
Epstein–Barr virus	Burkitt lymphoma
	AIDS-associated NHLs (especially CNS NHL, DLBCL)
	Posttransplant lymphoproliferative disorder
	Extranodal NK/T-cell NHL
Human herpesvirus 8	Primary effusion lymphoma and related DLBCLs
	MCD-associated plasmablastic NHL
Human T lymphotropic virus type I	Acute T-cell leukaemia/lymphoma
Agents that cause immunosuppression	
Human immunodeficiency virus	AIDS-associated NHLs
Agents that cause chronic immune stimulation	
Plasmodium falciparum	Burkitt lymphoma
Hepatitis C virus	DLBCL, lymphoplasmacytic NHL, marginal zone NHL
Hepatitis B virus	Uncertain
Helicobacter pylori	Gastric MALT NHL
Campylobacter jejuni	Small intestine MALT NHL
Chlamydia psittaci	Ocular adnexa MALT NHL
Borrelia burgdorferi	Cutaneous MALT NHL

NHL, non-Hodgkin lymphoma; AIDS, acquired immunodeficiency syndrome; CNS NHL, central nervous system non-Hodgkin lymphoma; DLBCL, diffuse large B cell lymphoma; MCD, multicentric Castleman disease; MALT, mucosa-associated lymphoid tissue.

Symposium

Journal of INTERNAL MEDICINE

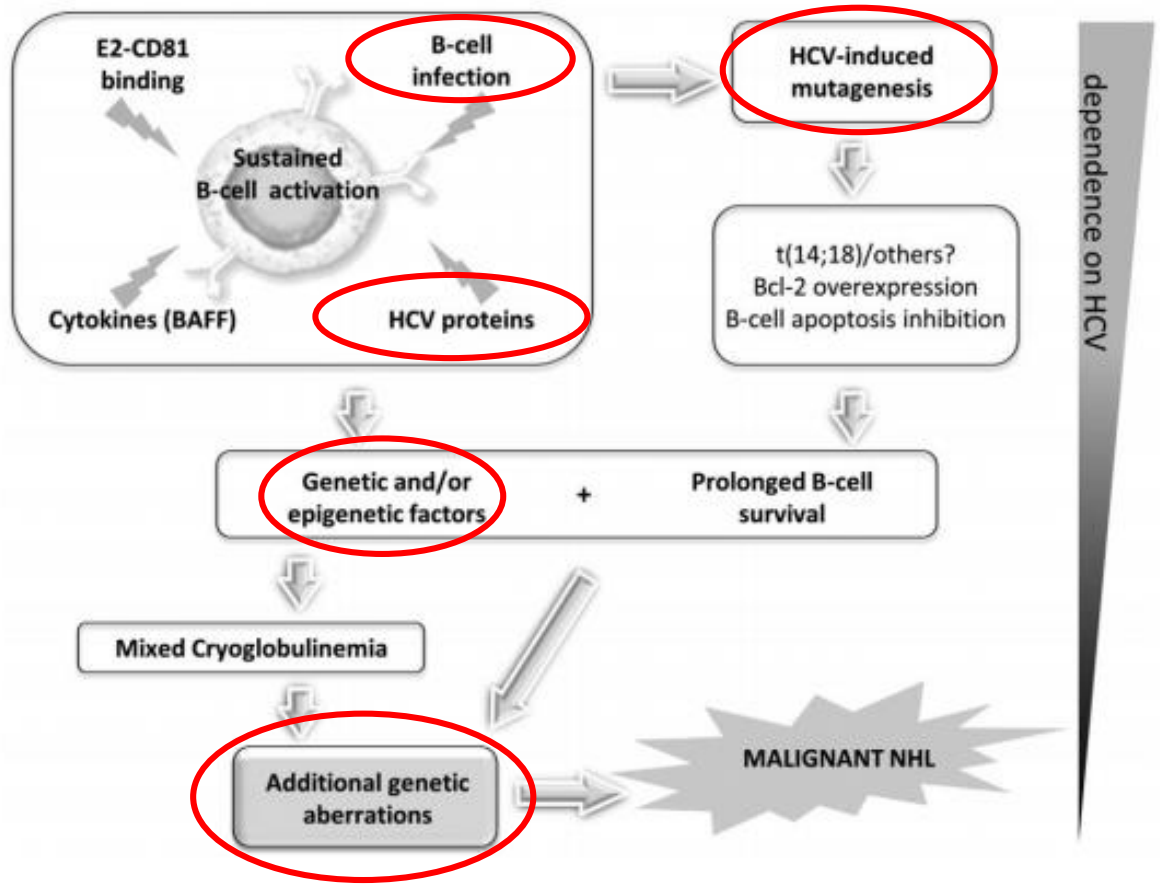
doi: 10.1111/j.1365-2796.2008.02031.x

Infectious aetiology of Hodgkin and non-Hodgkin lymphomas: a review of the epidemiological evidence

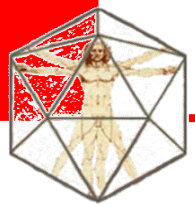
H. Hjalgrim[1] & E. A. Engels[2]

Hepatitis C virus	DLBCL, lymphoplasmacytic NHL, marginal zone NHL

HCV related LPDs: a multifactorial pathogenesis



Zignego AL, Autoimmunity Rev. 2017



The HCV lymphotropism

HCV lymphotropism

The ability of HCV to infect lymphoid cells was widely discussed.

- ✓ Technical problems in identifying HCV-RNA replicative intermediate in PBMCs;
- ✓ Extracellular HCV-RNA contamination.

Zignego AL et al. J Hepatol 1992; Zignego AL et al. J Med Virol 1995; Zignego AL et al DLD 2007.

HCV lymphotropism

nature COMMUNICATIONS

ARTICLE

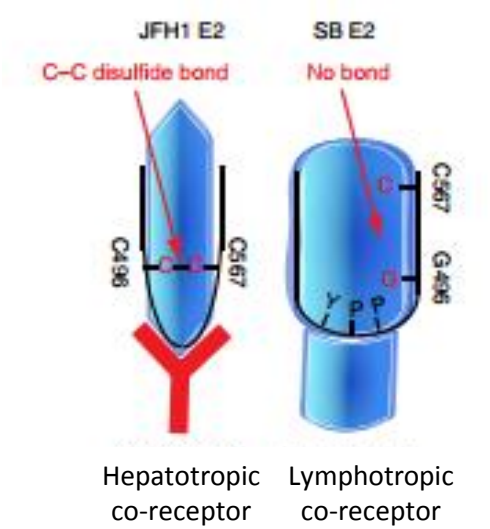
Received 16 Aug 2016 | Accepted 8 Nov 2016 | Published 9 Jan 2017

DOI: 10.1038/ncomms13882 OPEN

Hepatitis C virus has a genetically determined lymphotropism through co-receptor B7.2

Chia-Lin Chen[1], Jeffrey Y. Huang[1], Chun-Hsiang Wang[1], Stanley M. Tahara[1], Lin Zhou[1], Yasuteru Kondo[1], Joel Schechter[2], Lishan Su[3], Michael M.C. Lai[1,4], Takaji Wakita[5], François-Loïc Cosset[6], Jae U. Jung[1] & Keigo Machida[1]

Isolated from liver



Isolated from B cells

Hepatotropic co-receptor

Lymphotropic co-receptor

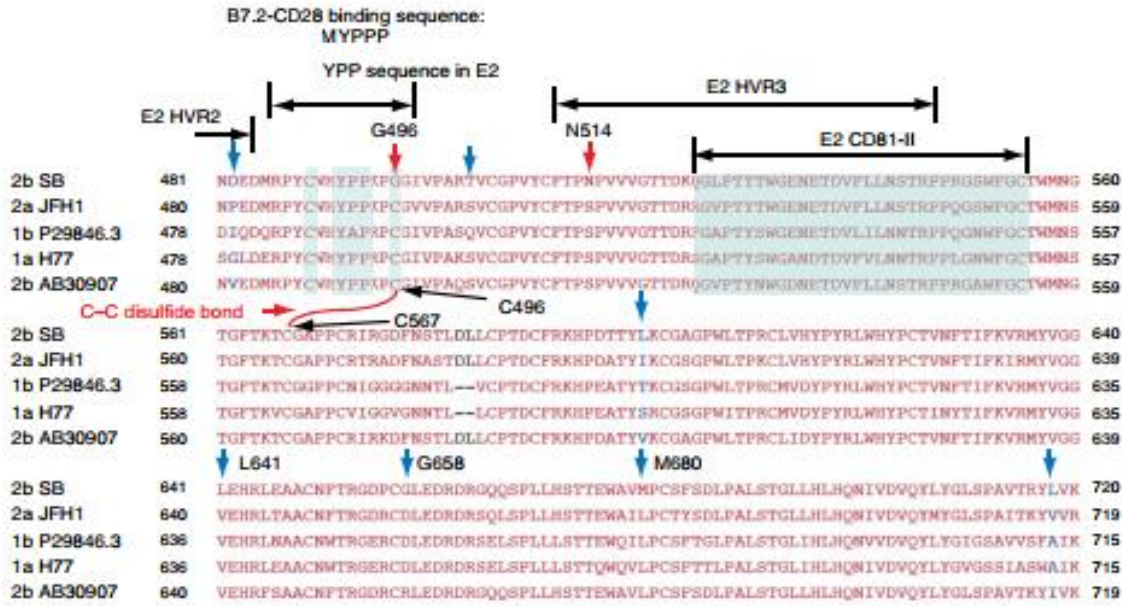
…from a lymphoma patient

HCV lymphotropism

Between the SB and JFH1 strains, were found:

- Differences in viral evelope sequence (coding for E1 and E2 proteins)
- Five nucleotide differences within 5' -UTR

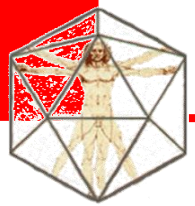
These differences mean that a specific HCV strain has a genetically determined lymphotropism



HCV lymphotropism

Summarizing...

- In this study, was established the genetic basis for lymphotropism of HCV infection;
- The viral envelope and 5' -UTR sequences of the lymphotropic HCV strain were responsible for the lymphotropism;
- B7.2 (CD86) is a co-receptor for observed HCV SB strain tropism towards memory B cell.

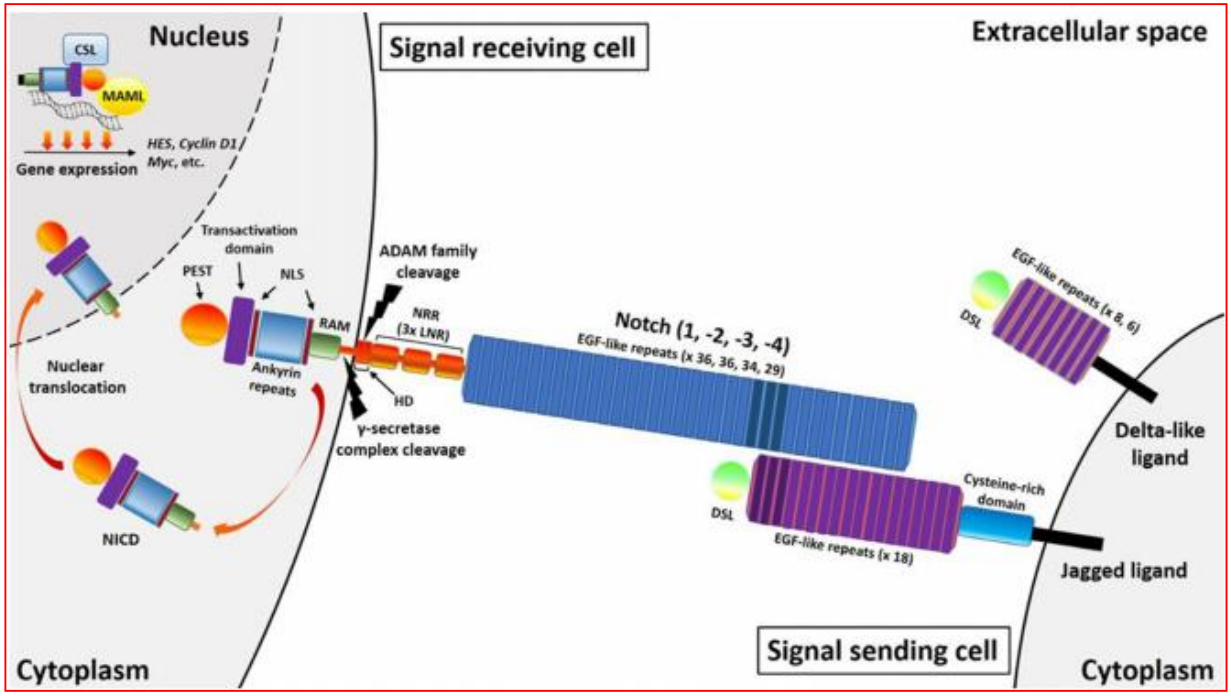


Notch family genes

NOTCH family

Notch is an evolutionally conserved signaling pathway consisting, in humans of a family of four transmembrane receptors and five ligands that allow cell-cell communication.

D'Souza et al, Curr Top Dev Biol 2010; Kovall et al, Curr Top Dev Biol 2010



From Gu Y *et al*, Oncotarget 2016

NOTCH family

- ✓ The role of Notch has been well characterized in the development of different tissues such as the processes of hematopoiesis and angiogenesis.

- ✓ This highly coordinated signaling system controls many aspects of cell biology, including differentiation, proliferation and death.

- ✓ Importantly, the role of aberrant Notch signaling, i.e. due to DNA mutations, was reported in hematological malignancies.

Karanu *et al*, Leukemia 2003; Pancewicz et al BMC cancer 2011; Vercauteren *et al*, Blood 2004; *Willander K, et al*, BMC Cancer 2013

Notch genes germ line and somatic mutations also seem to be involved in HCV-related lymphoma pathogenesis

A genome-wide association study




Genes and Immunity (2014), 1–6
© 2014 Macmillan Publishers Limited All rights reserved 1466-4879/14
www.nature.com/gene

ORIGINAL ARTICLE

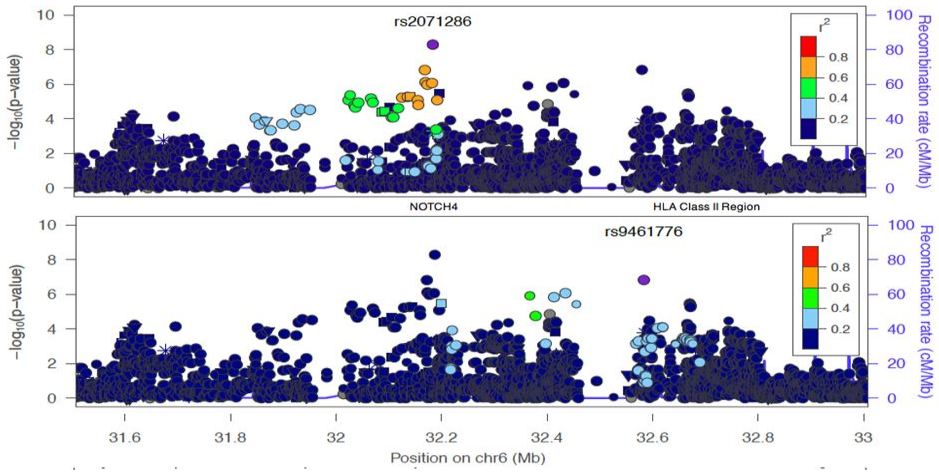
Genome-wide association study of hepatitis C virus- and cryoglobulin-related vasculitis

AL Zignego[1], GL Wojcik[2], P Cacoub[3,4,5,6], M Visentini[7], M Casato[7], A Mangia[8], R Latanich[9], ED Charles[10], L Gragnani[1], B Terrier[3], V Piazzola[8], LB Dustin[10,15], SI Khakoo[11], MP Busch[12], GM Lauer[13], AY Kim[13], L Alric[14], DL Thomas[9] and P Duggal[2]

- 899,641 markers from the Illumina HumanOmni1-Quad chip were analyzed
- 356 HCV RNA positive individuals with MC-related vasculitis
- 447 ethnically-matched, HCV RNA positive controls
- Replication of select SNPs was conducted using 91 cases and 180 controls

A genome-wide association study

chromosome 6 analysis



Independent signals are found at NOTCH4 and HLA-human leukocyte antigen -DRB1/DQA1

HLA-DRB1/DQA1-rs9461776

Each additional copy of the risk allele (G) was associated with 2.14 times the odds of MC-related vasculitis.

notch 4-rs2071286

The notch 4 (rs2071286) conferred 2.16 times the odds of having MC-related vasculitis

Zignego AL *et al*, Genes & Immunity 2014

NOTCH mutations in HCV-NHL: our experience

www.impactjournals.com/oncotarget/ Oncotarget, Advance Publications 2017

Notch4 and mhc class II polymorphisms are associated with hcv-related benign and malignant lymphoproliferative diseases

Laura Gragnani[1,*], Elisa Fognani[1,*], Valli De Re[2], Massimo Libra[3], Adriana Garozzo[3], Patrizio Caini[1], Guia Cerretelli[1], Andrea Giovannelli[1], Serena Lorini[1], Monica Monti[1], Silvia Bagnoli[4], Irene Piaceri[4], Anna Linda Zignego[1]

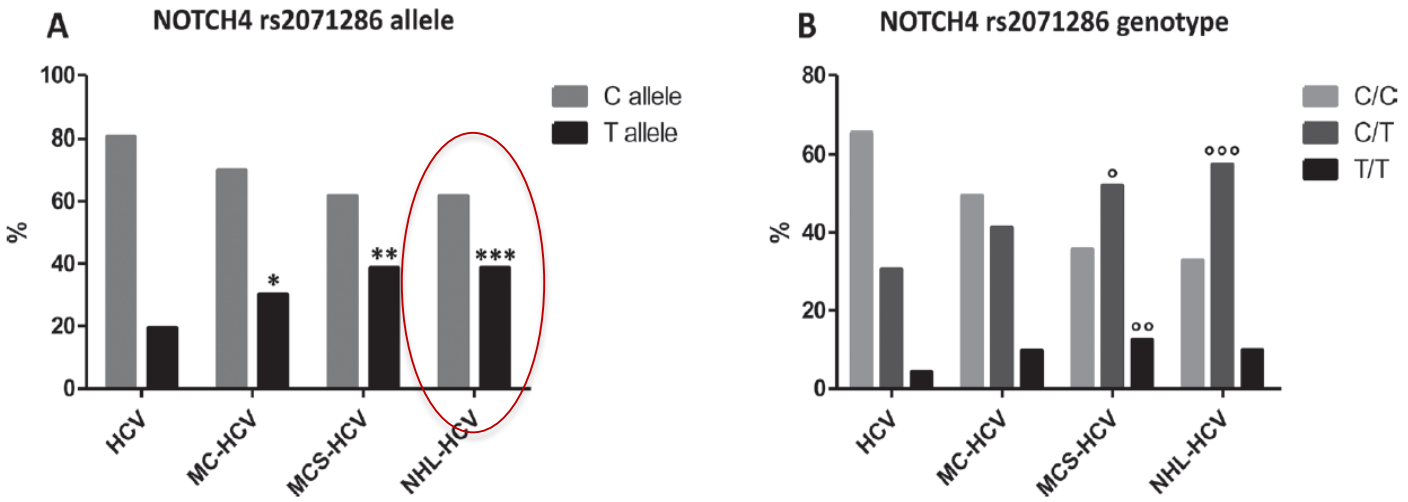


Figure 1: (Panel **A**) NOTCH4 rs2071286 allele frequency; *$p = 0.004$; **$p = 0.0002$; ***$p = 0.0006$; (Panel **B**) NOTCH4 rs2071286 genotype frequency; °$p = 0.008$; °°$p = 0.0122$; °°°$p = 0.006$.

- ✓ **Significant association between rs2071286 MAF with increased risk for NHL**
- ✓ **Potential usefulness as non-invasive lymphoma risk markers in HCV+ patients**

Gragnani L *et al*, Oncotarget 2017

NOTCH family mutations in lymphomas

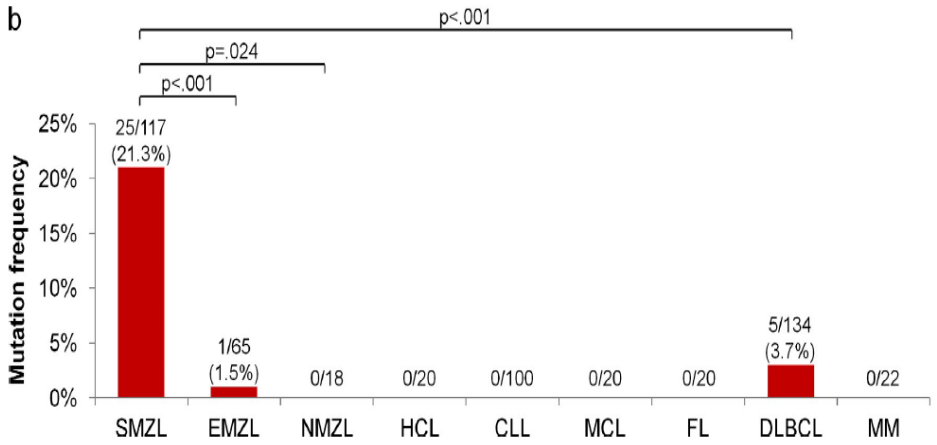
The coding genome of splenic marginal zone lymphoma: activation of *NOTCH2* and other pathways regulating marginal zone development

JEM

2012

Rossi D. et.

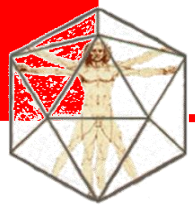
- ✓ **Mutations in NOTCH family genes have been found in 30% of SMZL cases**
- ✓ ***NOTCH2*, a gene required for marginal-zone (MZ) B cell development**
- ✓ ***NOTCH2* mutations are the most frequent lesions in SMZL, accounting for ~20% of cases**



***NOTCH2* mutations are specific for SMZL, very rare in DLBCL, not present in other histotypes**

NOTCH family mutations in HCV-lymphomas

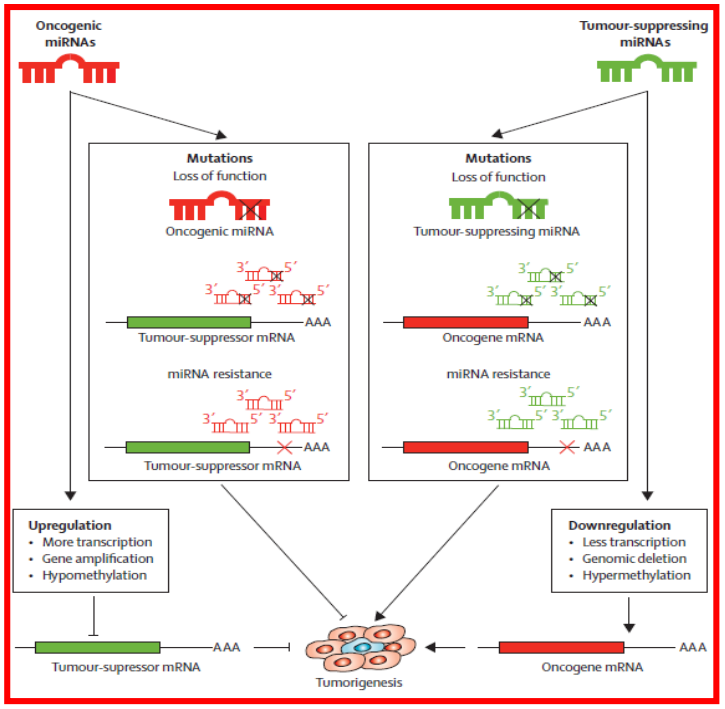
OVERALL, THIS DATA SUGGESTS THAT AT LEAST A FRACTION OF HCV-POSITIVE DLBCL MAY REPRESENT THE TRANSFORMED PHASE OF AN MZL CLONE OR THE COEXISTENCE OF HIGH AND LOW GRADE COMPONENTS.

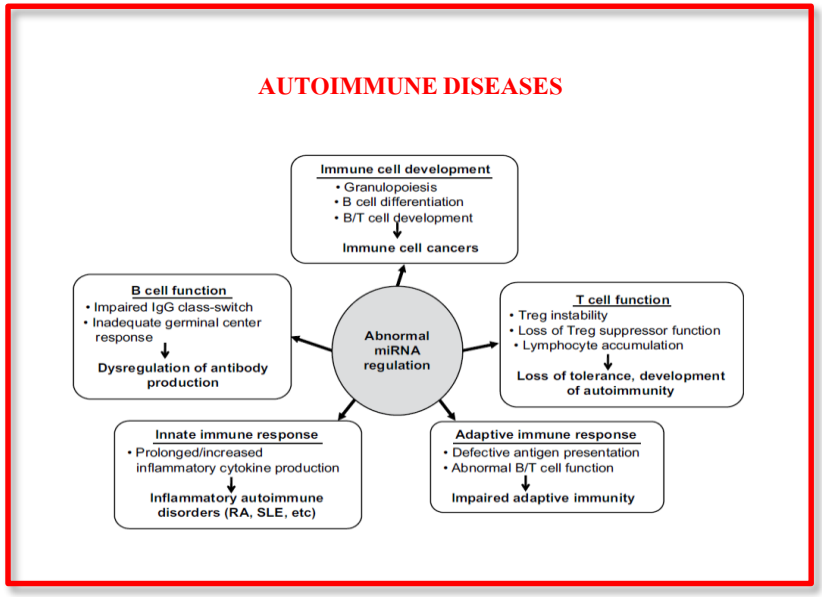


Epigenetic regulation: role of miRNAs

The epigenetic issue-the microRNAs

BINDING TO A COMPLEMENTARY mRNA OF A TARGET GENE THE microRNA INDUCES ITS DEGRADATION AND PREVENT THE FINAL PROTEIN EXPRESSION.





Pauley 2009, J. Autoimmunity

The epigenetic issue-the microRNAs

Dysregulation of global microRNA expression in splenic marginal zone lymphoma and influence of chronic hepatitis C virus infection

Leukemia, 2012

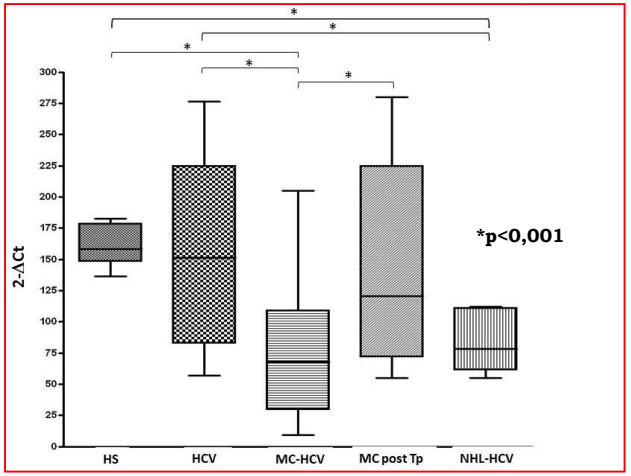
J Peveling-Oberhag[1,2], G Crisman[3], A Schmidt[4], C Döring[2], M Lucioni[5], L Arcaini[6], S Rattotti[6], S Hartmann[2], A Piiper[1], W-P Hofmann[1], M Paulli[6], R Küppers[4], S Zeuzem[1] and M-L Hansmann[2]

OUR EXPERIENCE:

The down-regulation of mir-26b in PBMC from both HCV-NHL and CV patients

&

the restoration of mir-26b levels after the virological and clinical resolution of CV



miR26-b

SUGGEST:

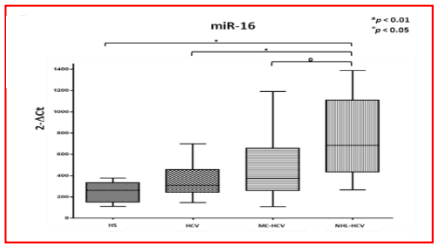
- **A role in pathogenesis of HCV-related lymphoproliferation**
- **A prognostic value (evolution/response to therapy)**

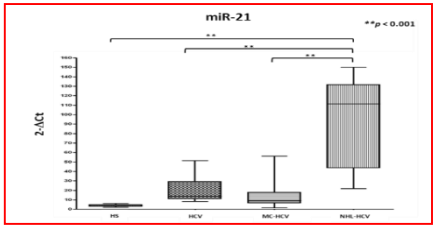
The epigenetic issue-the microRNAs

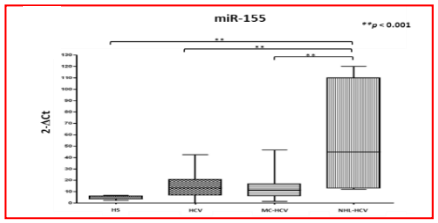
the up-regulation of

miR-16, miR-21 and miR-155

in PBMCs from HCV-NHL but not in HCV-CV and healthy subjects







***SUGGESTS*:**

- A role in HCV-related lymphomagenesis
- A prognostic value

Fognani et al, PlosOne 2013; Gragnani et al, J Hepatol 2013

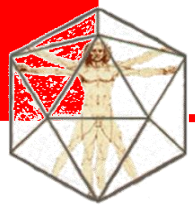
Summary of deregulated miRNAs

	CV	LYMPHOMA
miR-26b	●	●
miR-146	●	●
miR-155	●	●
miR-21	●	●
miR-16	●	●
miR-17	●	●
miR-18a	●	●
miR-19a	●	●
miR-19b	●	●
miR-20a	●	●
miR-92a	●	●

GREEN not deregulated compared to controls

RED deregulated (up- or down-) compared to controls

Chronic antigenic stimulation
&
The role of viral proteins



Chronic antigenic stimulation

HCV-related LPDs are characterized by the **clonal expansion of B-cell populations**, mostly in the liver and, less frequently, in the bone marrow or blood

Sansonno et al 1998; Racanelli et al. 2001

The similarities in rearranged Ig genes present in B-cells from MCS patients and from HCV B-cell NHL suggest that **the antigens involved in promoting type II MCS are the same as those involved in B-cell NHL development**

Ivanovski et al 1998; De Re et al. 2000

The HCV E2 and NS3 proteins were proposed as the potential antigens sustaining the expansion of B cell population in different LPDs

Quinn et al 2001; De Re et al. 2006

Chronic antigenic stimulation

blood

2014 123: 1512-1515
doi:10.1182/blood-2013-10-532895 originally published online January 21, 2014

B-cell receptors expressed by lymphomas of hepatitis C virus (HCV)–infected patients rarely react with the viral proteins

Patrick P. Ng, Chiung-Chi Kuo, Stanley Wang, Shirit Einav, Luca Arcaini, Marco Paulli, Carol S. Portlock, Joseph Marcotrigiano, Alexander Tarr, Jonathan Ball, Ronald Levy and Shoshana Levy

- ✓ seem to exclude the dependence of lymphoma cell BCR from viral antigens,
- ✓ confirmed that HCV positive lymphoma cells use a restricted repertoire of Ig variable genes;
- ✓ failed in attributing to their BCR a specificity against viral antigens.

HCV and BCR

OPEN

Oncogene

Oncogene (2016) **35,** 2979–2990

www.nature.com/onc

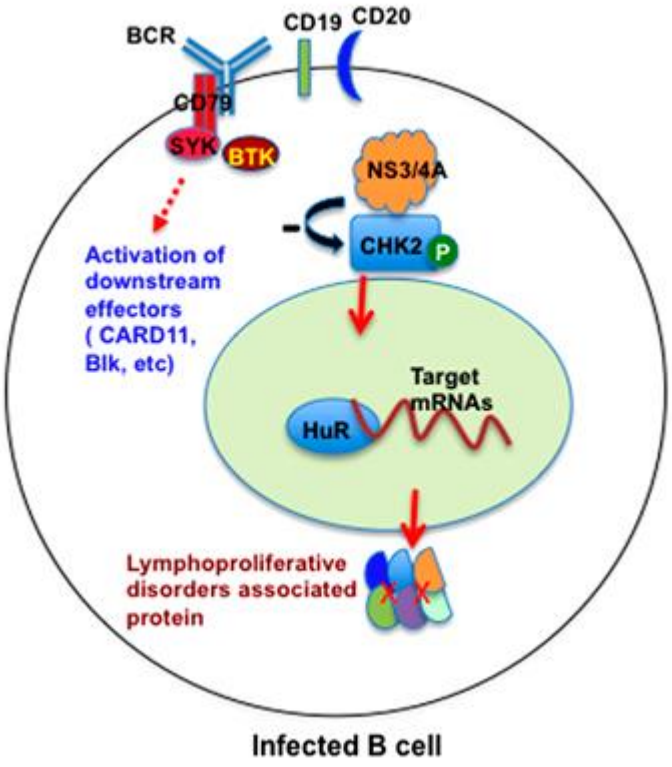
ORIGINAL ARTICLE

Hepatitis C virus upregulates B-cell receptor signaling: a novel mechanism for HCV-associated B-cell lymphoproliferative disorders

B Dai[1], AY Chen[2], CP Corkum[2], RJ Peroutka[1], A Landon[1], S Houng[1], PA Muniandy[1], Y Zhang[3], E Lehrmann[3], K Mazan-Mamczarz[1], J Steinhardt[1], M Shlyak[4], QC Chen[5], KG Becker[3], F Livak[1], TI Michalak[2], R Talwani[4] and RB Gartenhaus[1,6]

- ✓ Confirmed the expression of HCV viral proteins in B cells of HCV-infected patients;
- ✓ Show that HCV upregulates BCR signaling in human primary B cells.

Proposed mechanism for HCV B-cell LPDs



- ✓ HCV NS3 interacts with CHK2 and downregulates CHK2 activity;
- ✓ This repressed CHK2 activity modulates HuR posttranscriptional regulation of target mRNAs associated with B-cell LPDs, preferentially those involved in the BCR signaling pathway.

Chronic antigenic stimulation

OPEN

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- ✓ It is plausible that HCV potentially transforms cells by a 'hit and run' mechanism;
- ✓ HCV may initially stimulate B-cell proliferation;
- ✓ The transformed B cells no longer require continuous HCV stimulation and their BCRs may have undetectable reactivity with HCV.

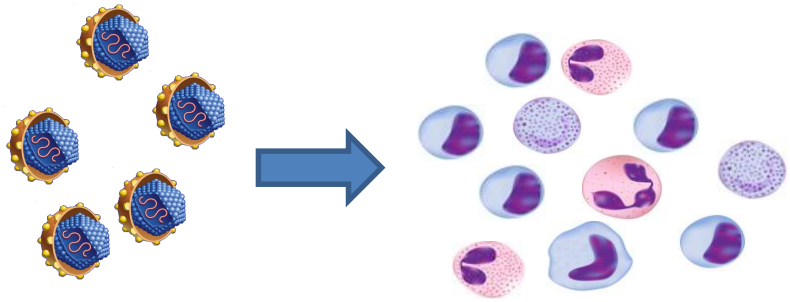
A direct oncogenic potential: an old *in vitro* study

PNAS

Hepatitis C virus induces a mutator phenotype: Enhanced mutations of immunoglobulin and protooncogenes

PNAS, 2004

Keigo Machida*, Kevin T.-N. Cheng*, Vicky M.-H. Sung*, Shigetaka Shimodaira*, Karen L. Lindsay†, Alexandra M. Levine†, Ming-Yang Lai‡, and Michael M. C. Lai*§



***in vitro* infection of different B-cell lines and PBMCs from donors**

HCV INFECTION INDUCES A MUTATOR PHENOTYPE

WHICH INVOLVES ENHANCED SOMATIC MUTATIONS OF MANY GENES.

How can HCV induce a mutator phenotype?

HCV INDUCES:

- **AN ERROR-PRONE DNA POLYMERASE**
- **ACTIVATION-INDUCED CYTIDINE DEAMINASE (AID)**

which together, contributed to the enhancement of mutation frequency

Mutation frequencies of cellular genes in HCV-infected cells

	HCV(−)*		HCV(+)	
Locus	Clones mutated†	Mutation frequency‡ × 10^{-4}	Clones mutated†	Mutation frequency‡ × 10^{-4}
V_H				
Raji	2/20	2.5	11/20	17.3
JT	1/20	1.2	6/20	9.9
BCL-6 (area B)				
Raji	0/20	0	8/20	8.3
JT	1/20	0.7	7/19	7.3
PBMC	2/54	0.8	27/80	6.4
PBMC (area A)	—	—	9/72	3.7
P53				
Raji	0/30	0§	4/30	6.7
JT	0/33	0	6/26	11.5
PBMC	1/172	0.3	36/400	4.6
β-catenin				
Raji	0/20	0	5/20	5.6
JT	0/19	0	6/18	7.4
PBMC	2/60	0.7	20/64	7.8
β-globin				
Raji	0/21	0	4/21	3.6
JT	0/24	0	6/24	4.7
PBMC	1/56	0.6	8/58	4.2

HCV MAY CAUSE TUMOR FORMATION BY A HIT-AND-RUN MECHANISM.

Machida K *et al*, PNAS 2004

HCV direct oncogenic potential - *in vivo* studies

Persistent expression of the full genome of hepatitis C virus in B cells induces spontaneous development of B-cell lymphomas in vivo

*Yuri Kasama,[1] *Satoshi Sekiguchi,[2] Makoto Saito,[1] Kousuke Tanaka,[1] Masaaki Satoh,[1] Kazuhiko Kuwahara,[3] Nobuo Sakaguchi,[3] Motohiro Takeya,[4] Yoichi Hiasa,[5] Michinori Kohara,[2] and Kyoko Tsukiyama-Kohara[1]

blood
2010

TRANSGENIC MICE EXPRESSING:

- ✓ **full length of viral genome (all the HCV proteins)**
- ✓ **expressed only in B-lymphocytes (cre-lox mice)**
- ✓ **under control of CD19 promoter**

SHOWED A 25% INCIDENCE OF DLBCL

Summarizing the *in vivo*-studies…

Review Article

Hepatitis C Virus-Related Lymphomagenesis in a Mouse Model

Kyoko Tsukiyama-Kohara,[1] Satoshi Sekiguchi,[2] Yuri Kasama,[1]
Nagla Elwy Salem,[1,3,4] Keigo Machida,[5] and Michinori Kohara[2]

ISRN Haematology, 2011

- **extremely high incidences of lymphomas and lymphoproliferative disorders;**
- **expression of HCV genes in all the lymphoma cells;**
- **increased levels of BCL-2 expression, which promoted oncogenic transformation of lymphocytes;**
- **increased levels of interleukin 10 and 2 (IL-10 & IL-2).**

A direct role of NS3 protein in human NHL

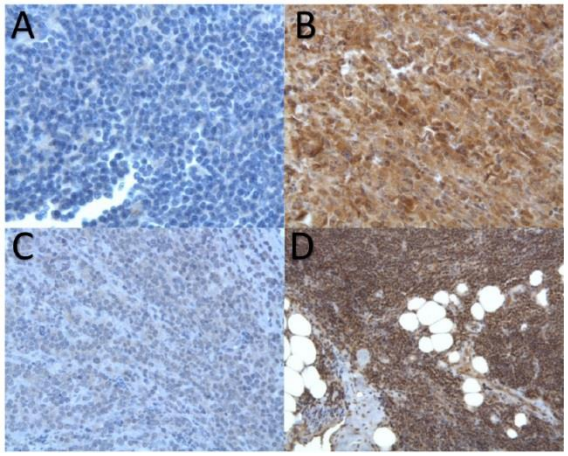
NEGATIVE STAINING: MZL

STRONG STAINING: DLBCL

PLOS ONE 2016

In Situ Hepatitis C NS3 Protein Detection Is Associated with High Grade Features in Hepatitis C-Associated B-Cell Non-Hodgkin Lymphomas

Danielle Canioni[1☯*], Jean-Marie Michot[2☯], Pascaline Rabiega[3], Thierry J. Molina[1], Frédéric Charlotte[4], Thierry Lazure[5], Frédéric Davi[6], Catherine Settegrana[6], Françoise Berger[7], Laurent Alric[8], Patrice Cacoub[9], Benjamin Terrier[9], Felipe Suarez[10,11], David Sibon[10,11], Jehan Dupuis[12], Cyrille Feray[13], Hervé Tilly[14], Stanislas Pol[15], Bénédicte Deau Fischer[16], Sandrine Roulland[17], Catherine Thieblemont[18], Véronique Leblond[19], Fabrice Carrat[3], Olivier Hermine[10,11‡*], Caroline Besson[20‡*], national ANRS HC13 LymphoC study[¶]



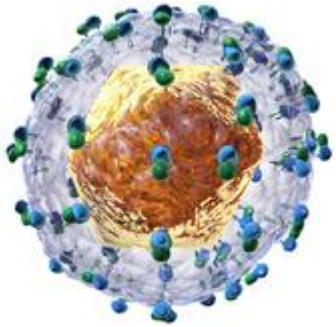
WEAK STAINING: MZL

STRONG STAINING: MZL ENRICHED IN LARGE CELLS

- ✓ In situ expression of the oncogenic HCV NS3 protein on HCV patients with B-NHL (DLBCL and MZL)
- ✓ NS3 immunostaining positive in 12/14 DLBCL vs only 4/14 MZL ($p = 0.006$); moreover, 2/4 NS3+ MZL were enriched in large cells

This study supports a new mechanism of transformation with a direct oncogenic role of HCV proteins in the occurrence of high-grade B lymphomas

Three different pictures:



MZL (low grade)

USUALLY EFFECTIVE

De novo DLBCL (high grade)

PLUS R-CHOP

DLBCL (high grade) transformed from MZL (low grade)

PLUS R-CHOP

Thank you for your attention!