

Enfermedades hepáticas mediadas por el sistema inmunitario

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CHU Sainte-Justine
*Le centre hospitalier
universitaire mère-enfant*

Pour l'amour des enfants

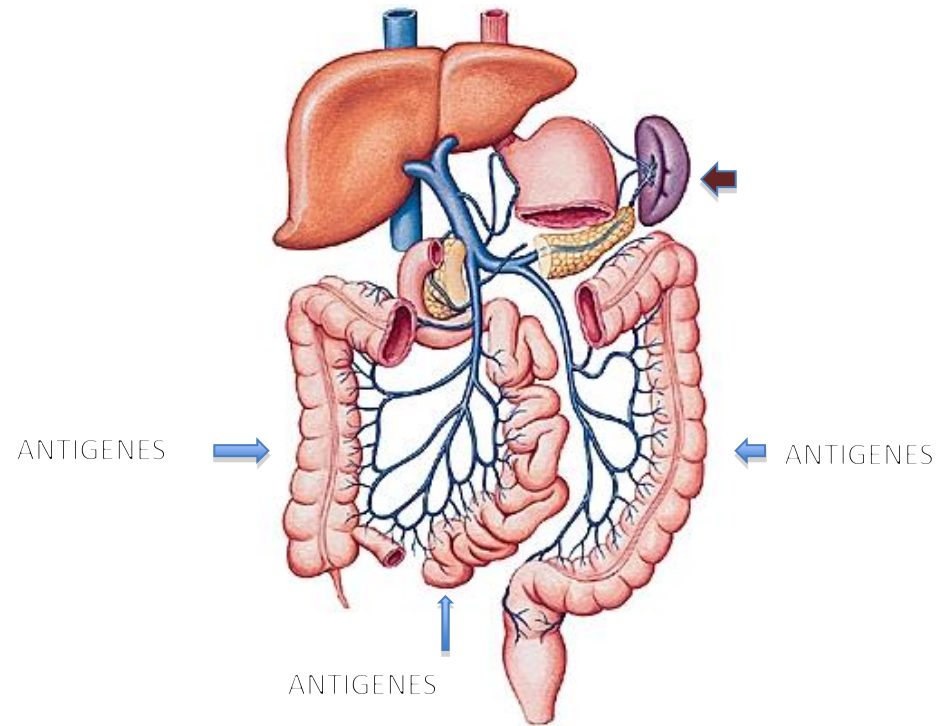
Université 
de Montréal

Enfermedades hepáticas mediadas por el sistema inmunitario

¿« Es el hígado un organo del sistema inmunitario »?

HIGADO Y SISTEMA INMUNITARIO

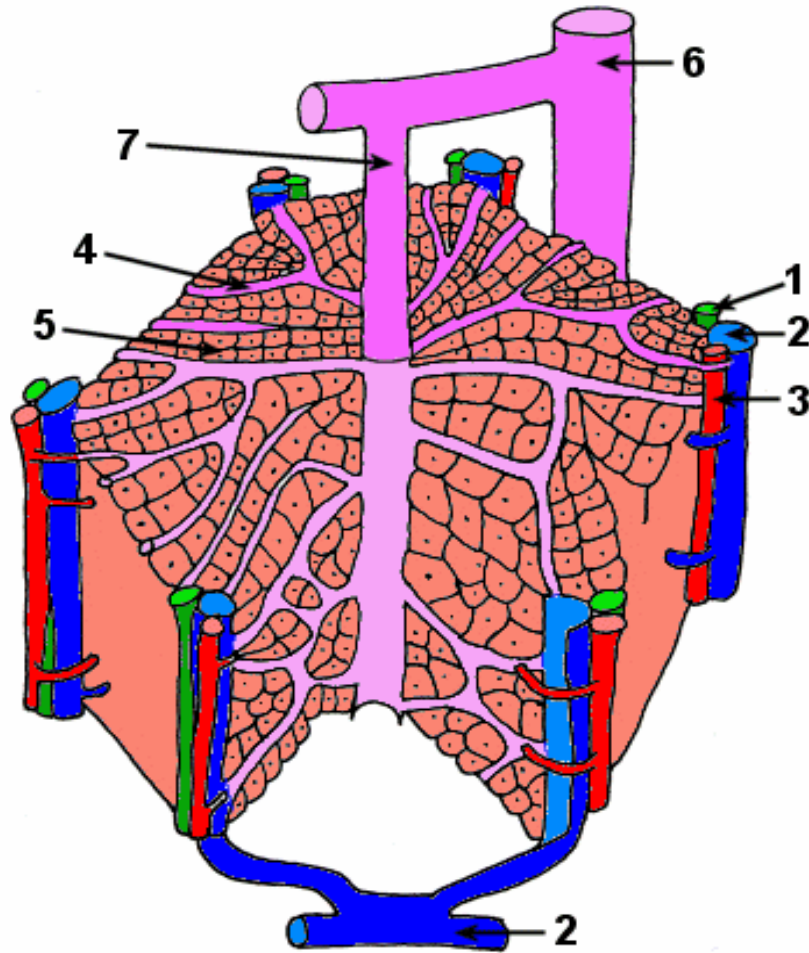
CIRCULACION HEPATICA



TOLERANCIA VS RESPUESTA INMUNITARIA

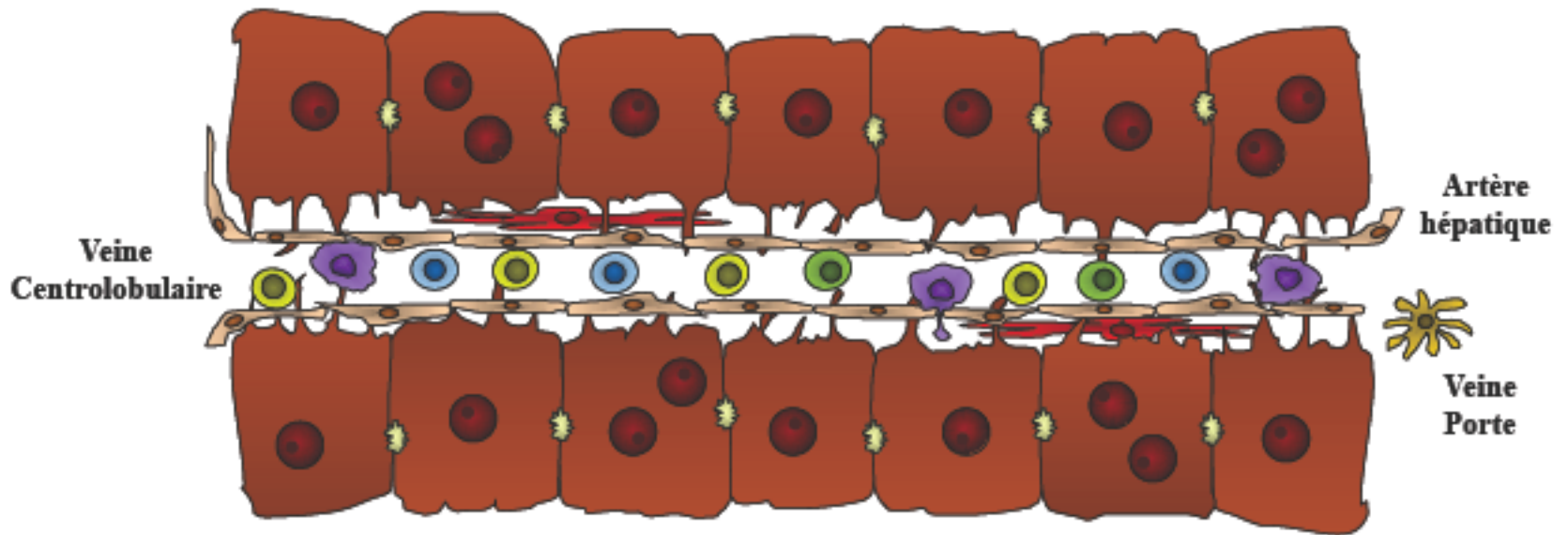
HIGADO Y SISTEMA INMUNITARIO

CIRCULACION HEPATICA

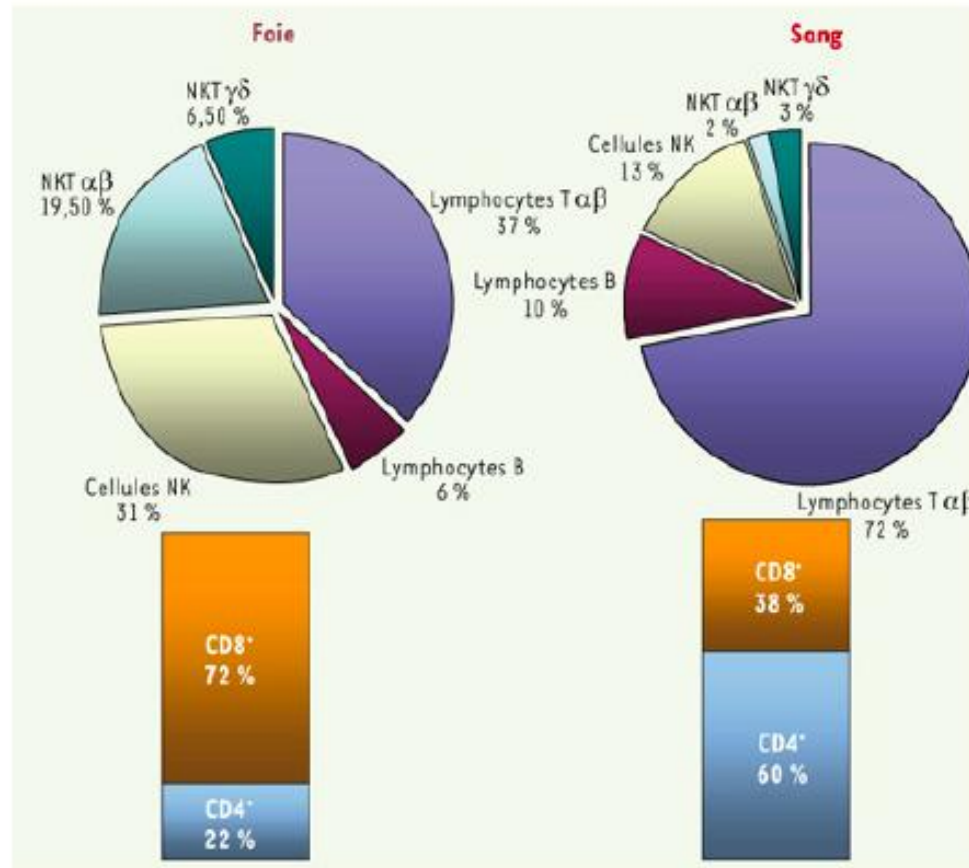


HIGADO Y SISTEMA INMUNITARIO

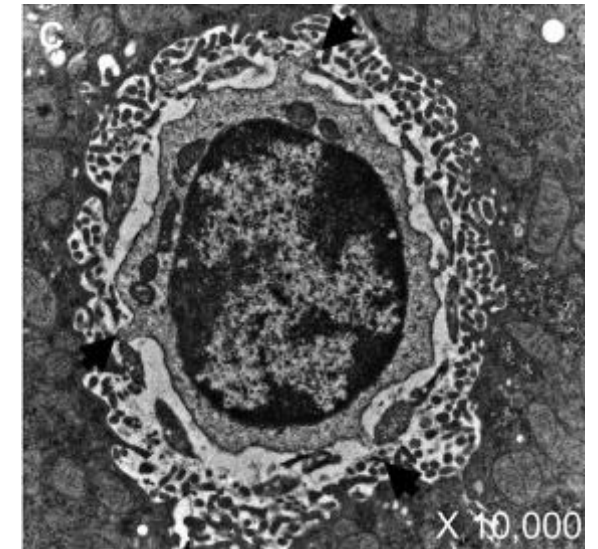
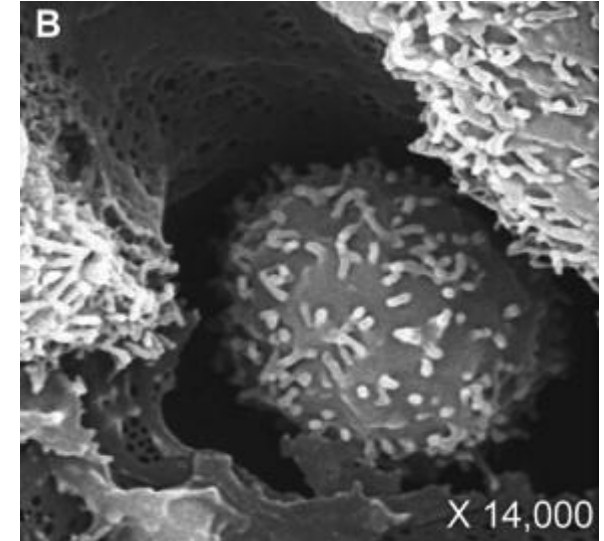
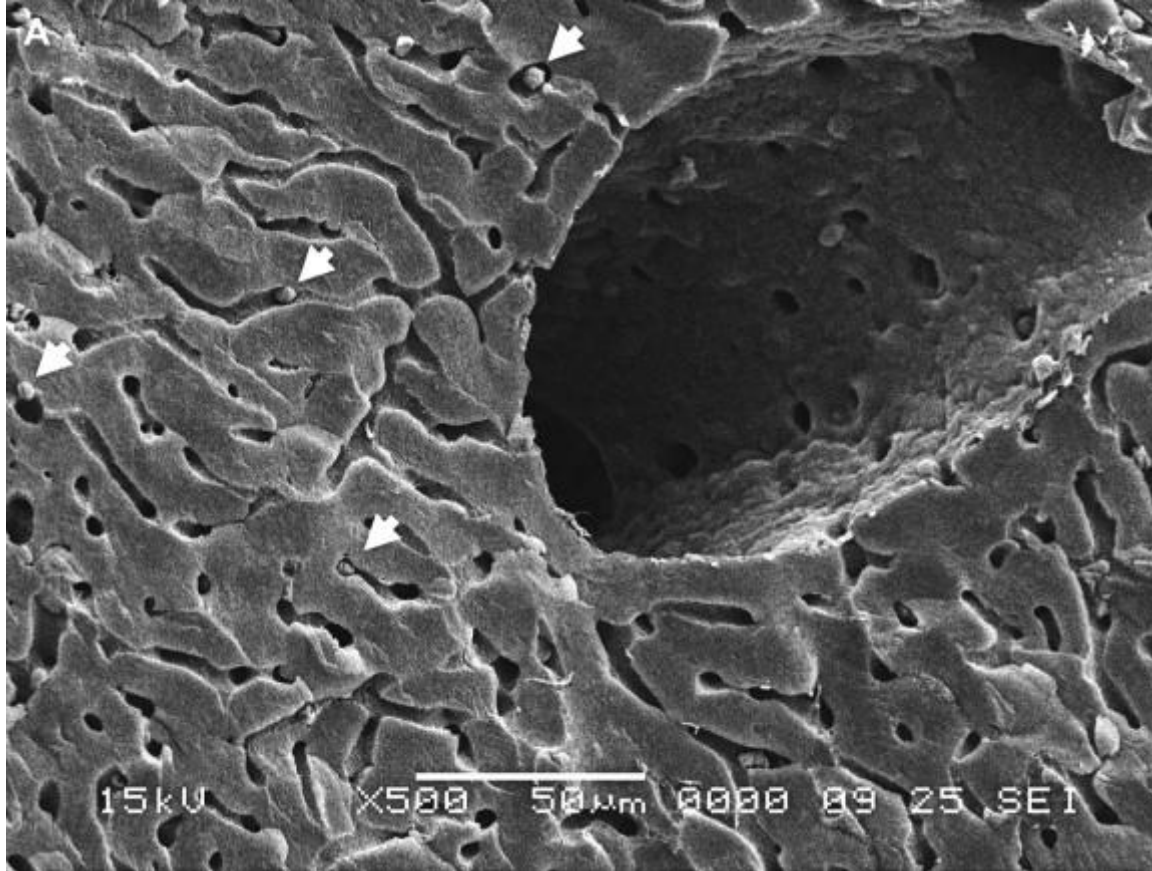
CIRCULACION HEPATICA



HIGADO Y SISTEMA INMUNITARIO



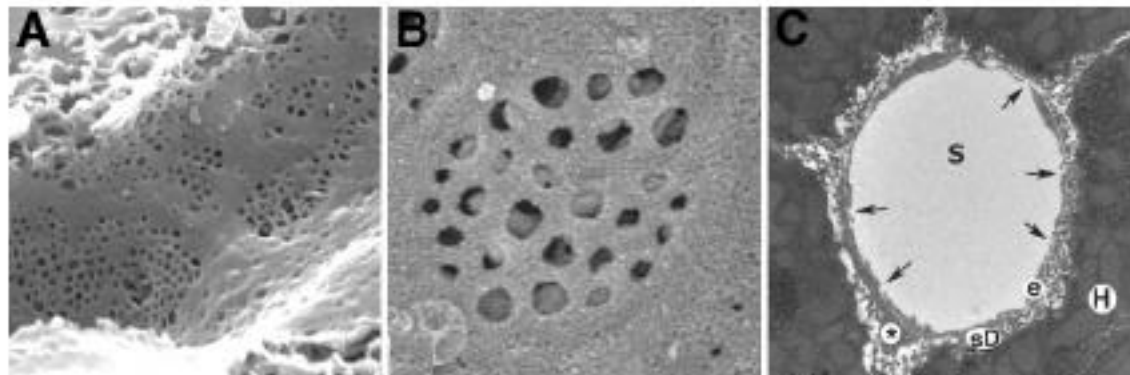
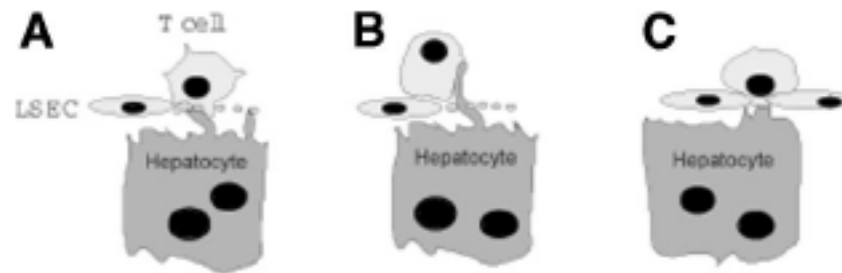
HIGADO Y SISTEMA INMUNITARIO



Electron micrographs of the hepatic sinusoids. A) Scanning electron micrograph showing a low power magnification of the liver sinusoids. Leucocytes circulating in the lumen are indicated by an arrow. B) Scanning electron micrograph showing a leucocyte engaged in the sinusoids. C) Transmission electron micrograph of a lymphocyte anchored in the sinusoid and interacting with hepatocytes (arrows).

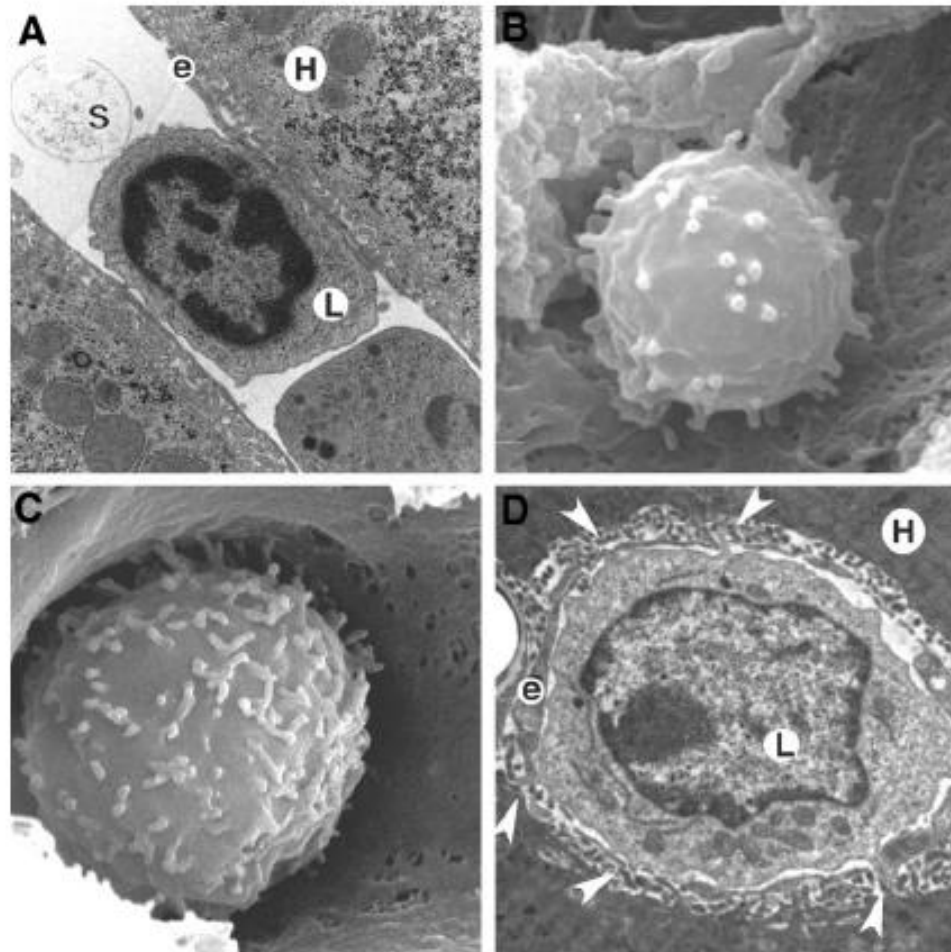
T Lymphocytes Interact With Hepatocytes Through Fenestrations in Murine Liver Sinusoidal Endothelial Cells

Alessandra Warren,¹ David G. Le Couteur,¹ Robin Fraser,² David G. Bowen,³
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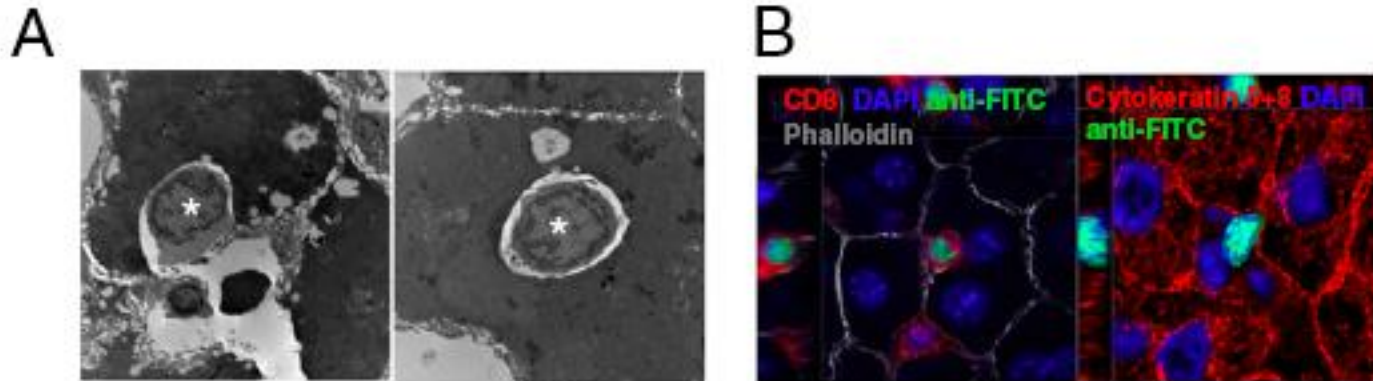
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HIGADO Y SISTEMA INMUNITARIO

EMPERIPOLESIS



Proc Natl Acad Sci U S A. 2011 Oct 4;108(40):16735-40.

Hepatocyte entry leads to degradation of autoreactive CD8 T cells.

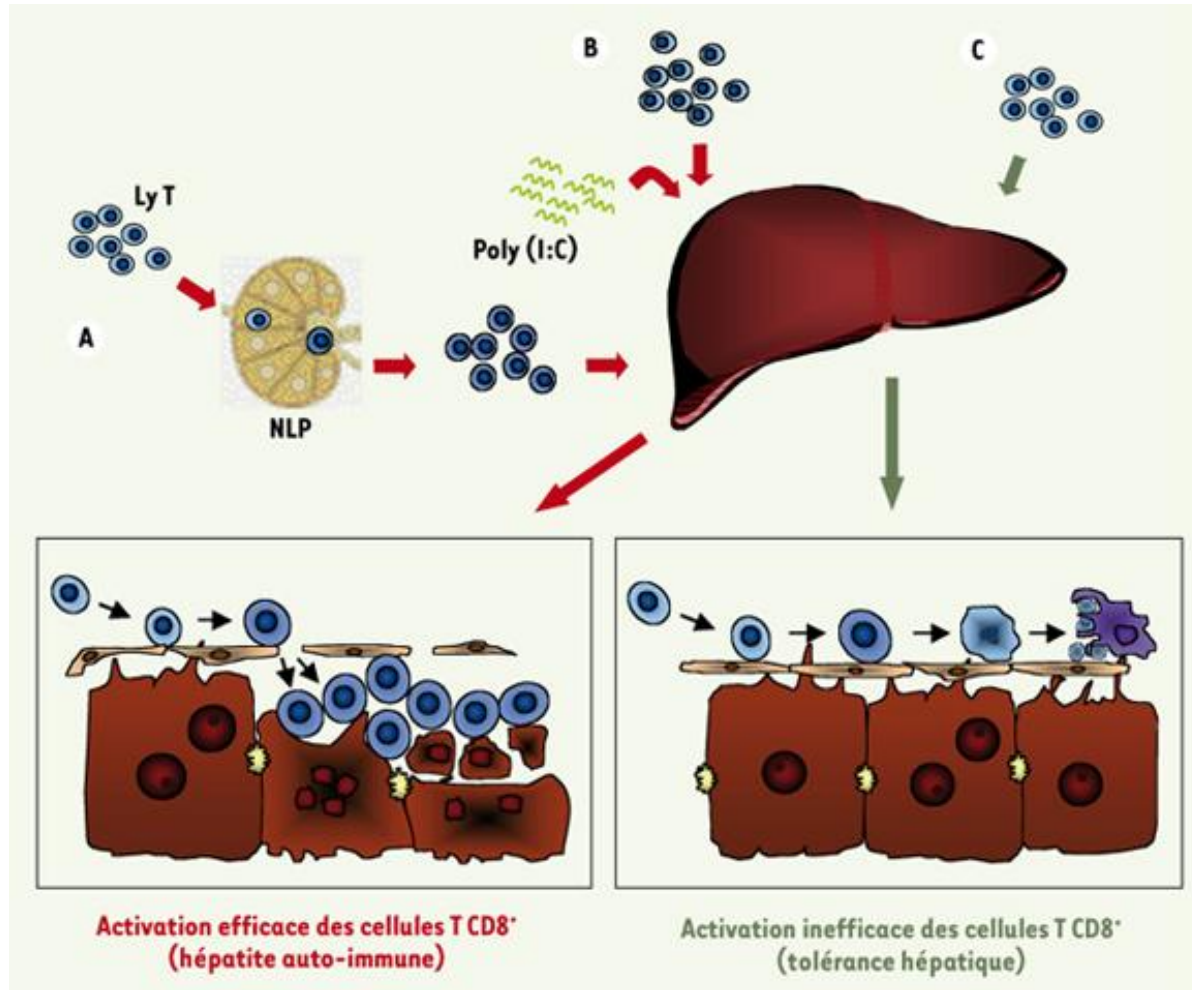
Benseler V, Warren A, Vo M, Holz LE, Tay SS, Le Couteur DG, Breen E, Allison AC, van Rooijen N, McGuffog C, Schlitt HJ, Bowen DG, McCaughan GW, Bertolino

. Immune mediated hepatic injury. Classification by main immune mechanism responsible of the disease.

Mechanism	Disease
Antibody mediated	• Fetal alloimmune hepatitis
	• Giant cell hepatitis with autoimmune hemolytic anemia (90)
	• Rejection (anti-HLA alloantibodies)*
T-cell mediated	• AIH
	• PBC
	• SC
	• Graft vs Host
	• Cellular rejection
Cytokines/Apoptosis	• Virus infections
	• Drugs toxicity
	• Bystander hepatitis

* This mechanism remains controversial in liver transplanted patients

Enfermedades hepáticas mediadas por el sistema inmunitario (células T)



- A. HEPATITE AUTOIMMUNE
- B. HEPATITE AUTOIMMUNE OU ELIMINATION
- C. ELIMINATION

Enfermedades hepáticas mediadas por el sistema inmunitario

1) Enfermedades provocadas por células T:

» - HAI

» - Colangitis esclerosante

» - Cirrosis biliar primitiva

» - Injerto vs huesped

» - Rechazo celular

» - Infecciones virales

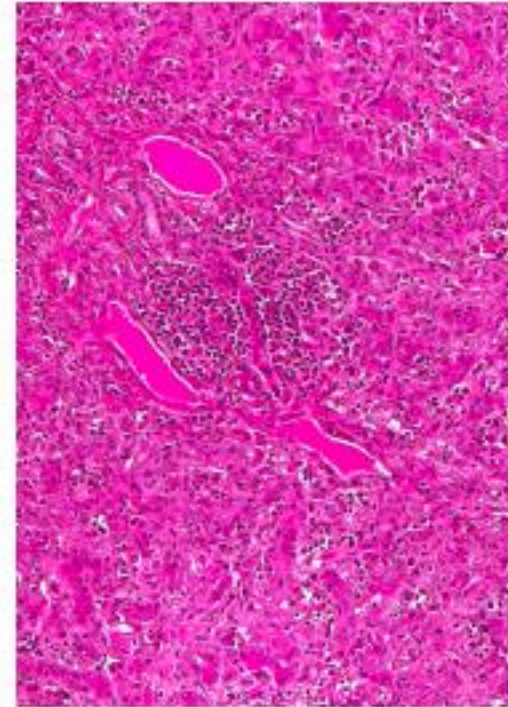
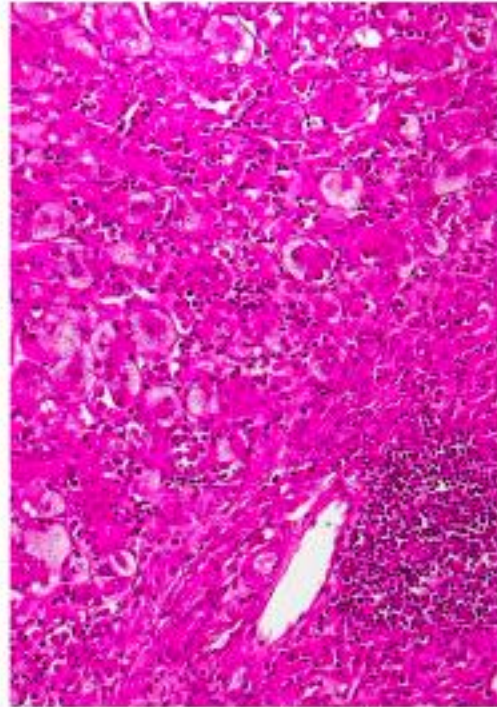
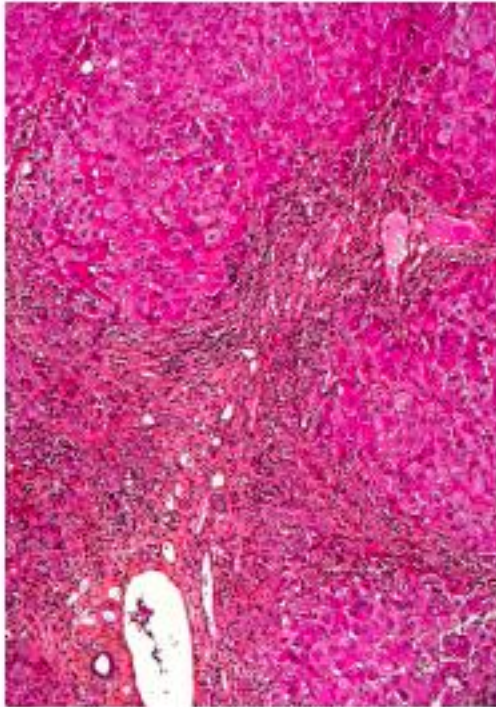
» - Hepatitis tóxica

HEPATITIS AUTOINMUNE

Criterios clinicos y de laboratorio que ayudan al diagnostico

- ✦ **Sexo femenino**
- ✦ **AP/AST < 1.5**
- ✦ **Globulinas séricas (IgG) elevadas**
- ✦ **Autoanticuerpos (ANA, SMA, LKM1, LC1)**
- ✦ **Marcadores de hepatitis viral negativos**
- ✦ **No drogas**
- ✦ **Otras enf. autoinmunes**
- ✦ **Características histológicas**
- ✦ **Respuesta completa al tratamiento**

Hepatitis autoinmune-Histología



HEPATITIS AUTOINMUNE

Tipos de HAI

Autoantibody	Antigen	Type 1 AIH	Type 2 AIH
SMA	Actin filaments	(90-100%)	
ANA	Various	+ (0-10%)	
SMA/ANA		+ (40-60%)	
LKM1	Cytochrome P450 2D6		+ (40-50%)
LC1	Formiminotransferase cyclodeaminase		+ (10-15%)
LKM1/LC1			+ (35-45%)
SLA	tRNP ^(Ser) See	+ (50%)	
ASGP-R	Asialo-glycoprotein receptor	+ (75%)	

. Extrahepatic autoimmune/immune mediated diseases
in patients with autoimmune hepatitis.

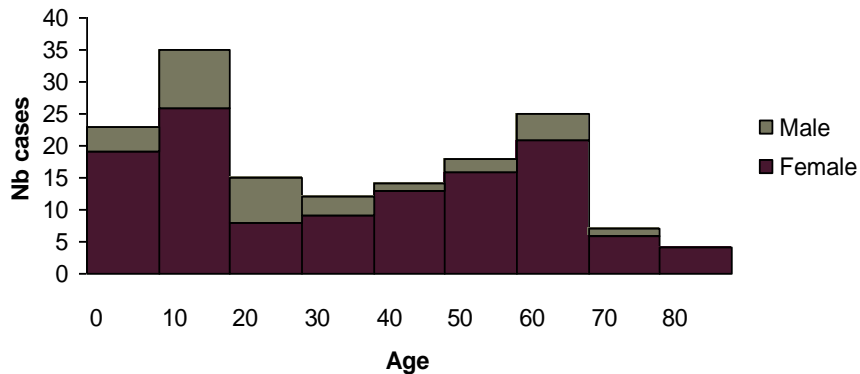
	Common	Rare
AIH type 1	<ul style="list-style-type: none"> Ulcerative colitis Vasculitis Arthritis Polymorphous erythema Hypergammaglobulineamic purpura Autoimmune thrombocytopenia Autoimmune hemolytic anemia* Glomerulonephritis* 	<ul style="list-style-type: none"> Fibrosing alveolitis
AIH type 2	<ul style="list-style-type: none"> Vitiligo Alopecia areata Nail dystrophy Pyoderma gangrenosum Thyroiditis* Diabetes* 	<ul style="list-style-type: none"> Autoimmune lymphoproliferative syndrome Autoimmune enteropathy IPEX APECED STAT1 deficiency

* These autoimmune diseases could be observed in both AIH types

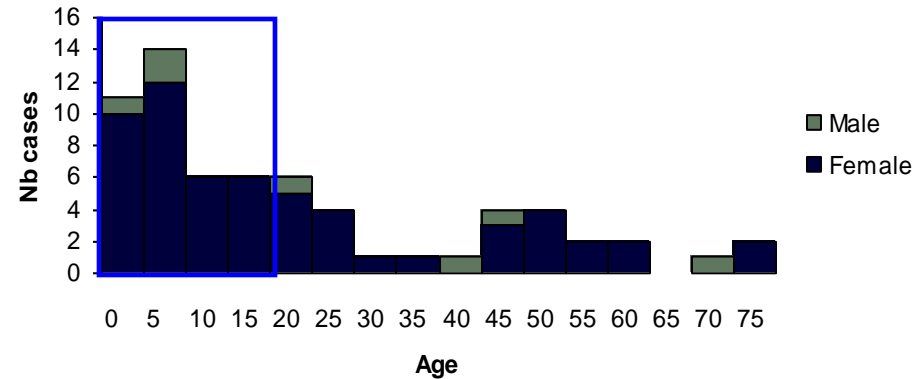
AUTOIMMUNE HEPATITIS

THE INFLUENCE OF AGE AND SEX

Type 1 autoimmune hepatitis



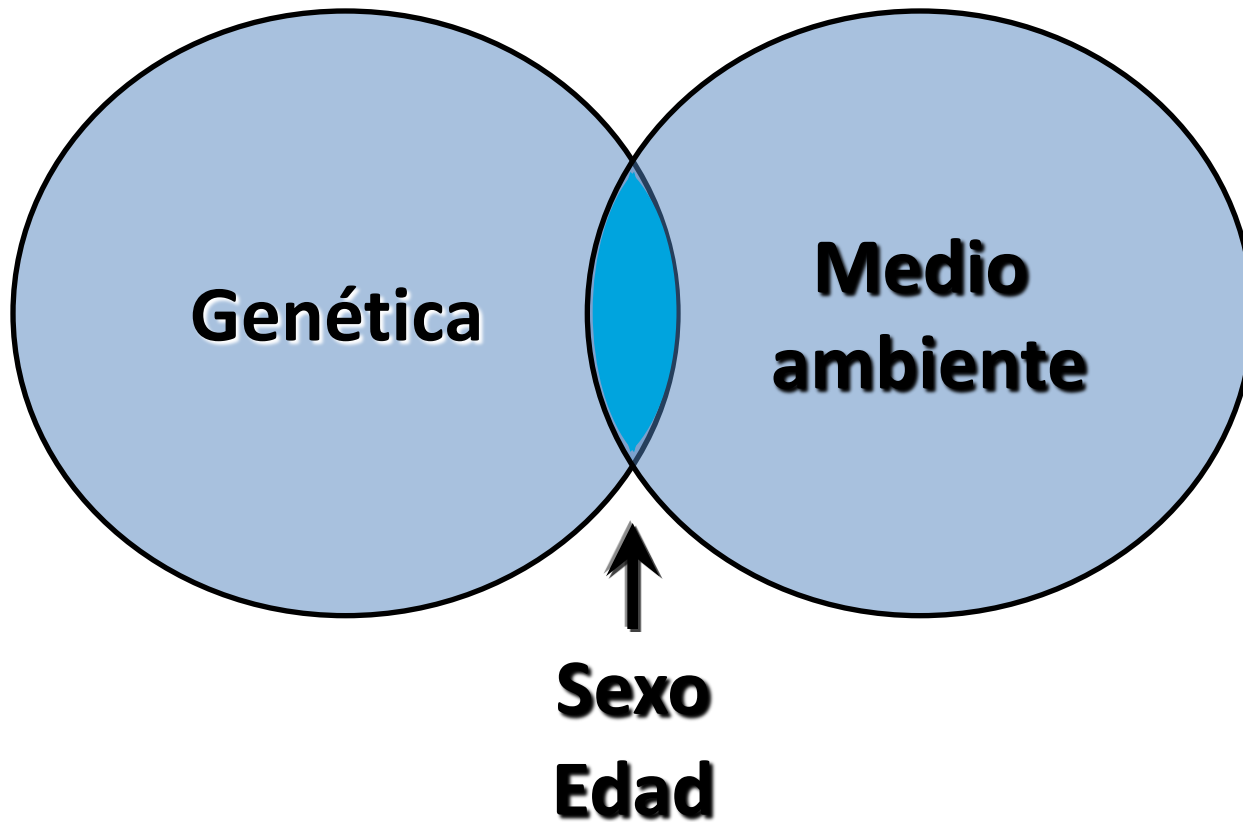
Type 2 Autoimmune hepatitis



- Almost 90% of type 2 AIH cases are females and more than 80% are diagnosed before the age of 18

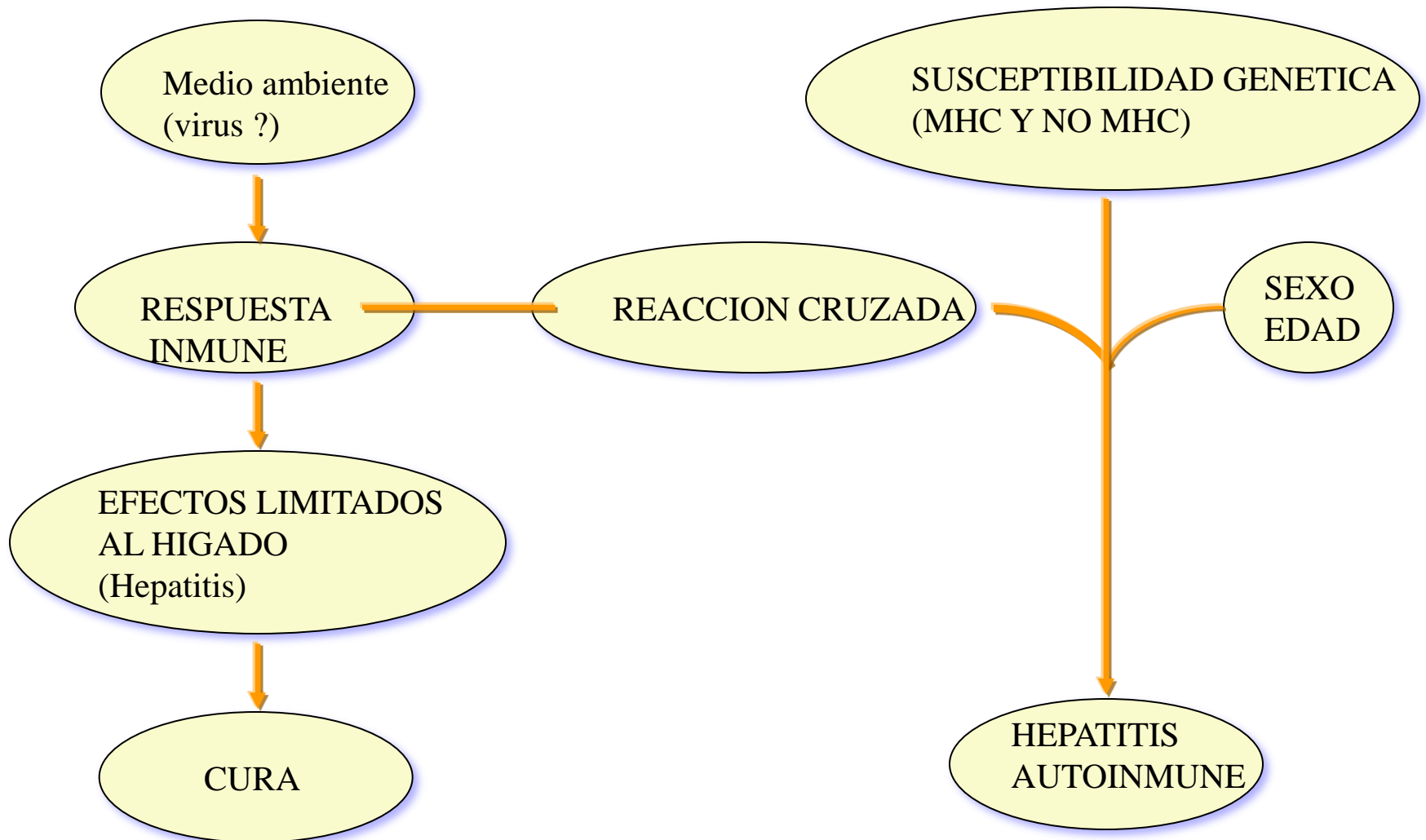
Hepatitis Autoinmune

Patogénesis

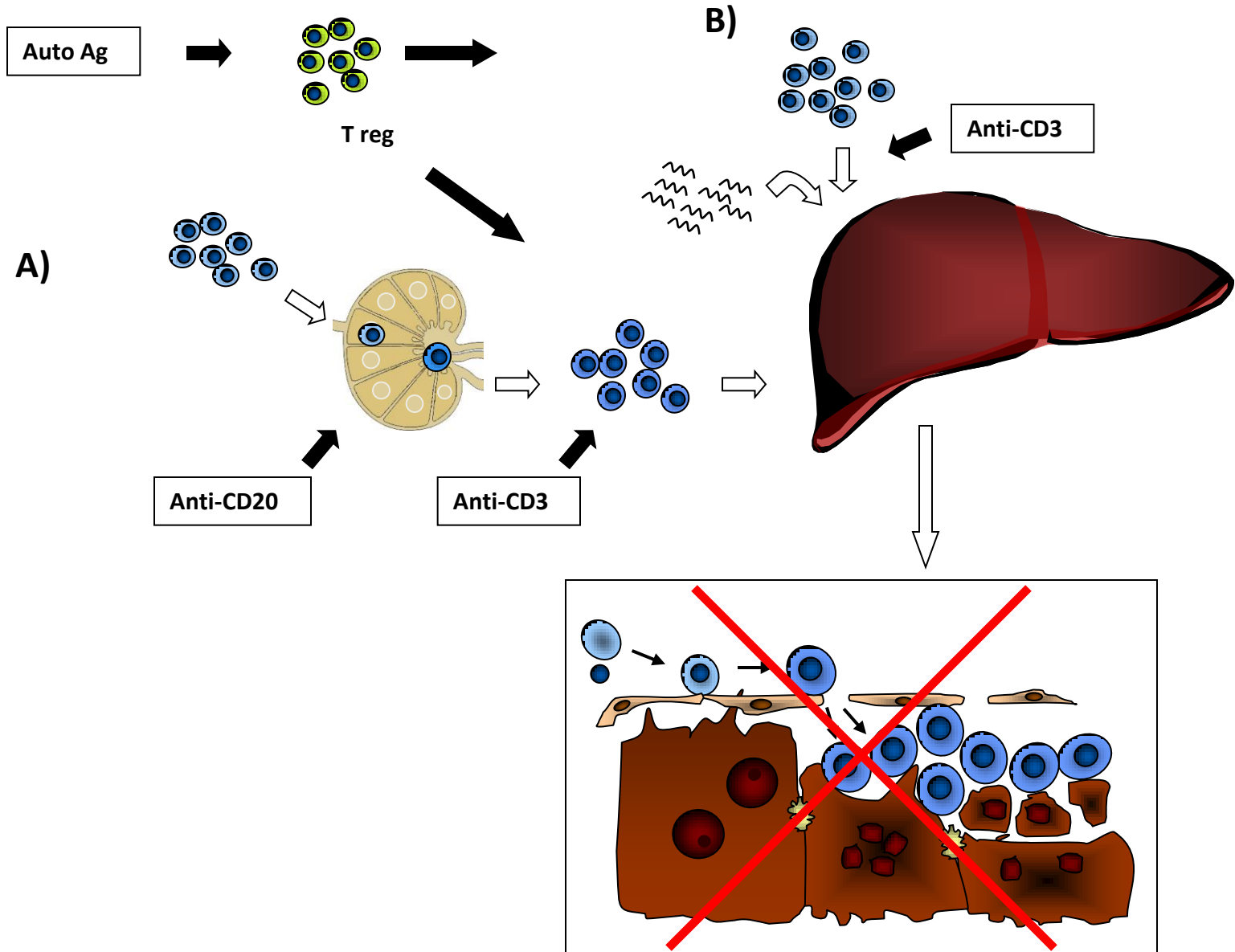


HEPATITIS AUTOINMUNE

Patogénesis



Autoimmune hepatitis - Pathogenesis



Enfermedades hepáticas mediadas por el sistema inmunitario

Enfermedades provocadas por células T:

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» - Colangitis esclerosante

» - Cirrosis biliar primitiva

» - Injerto vs huesped

» - Rechazo celular

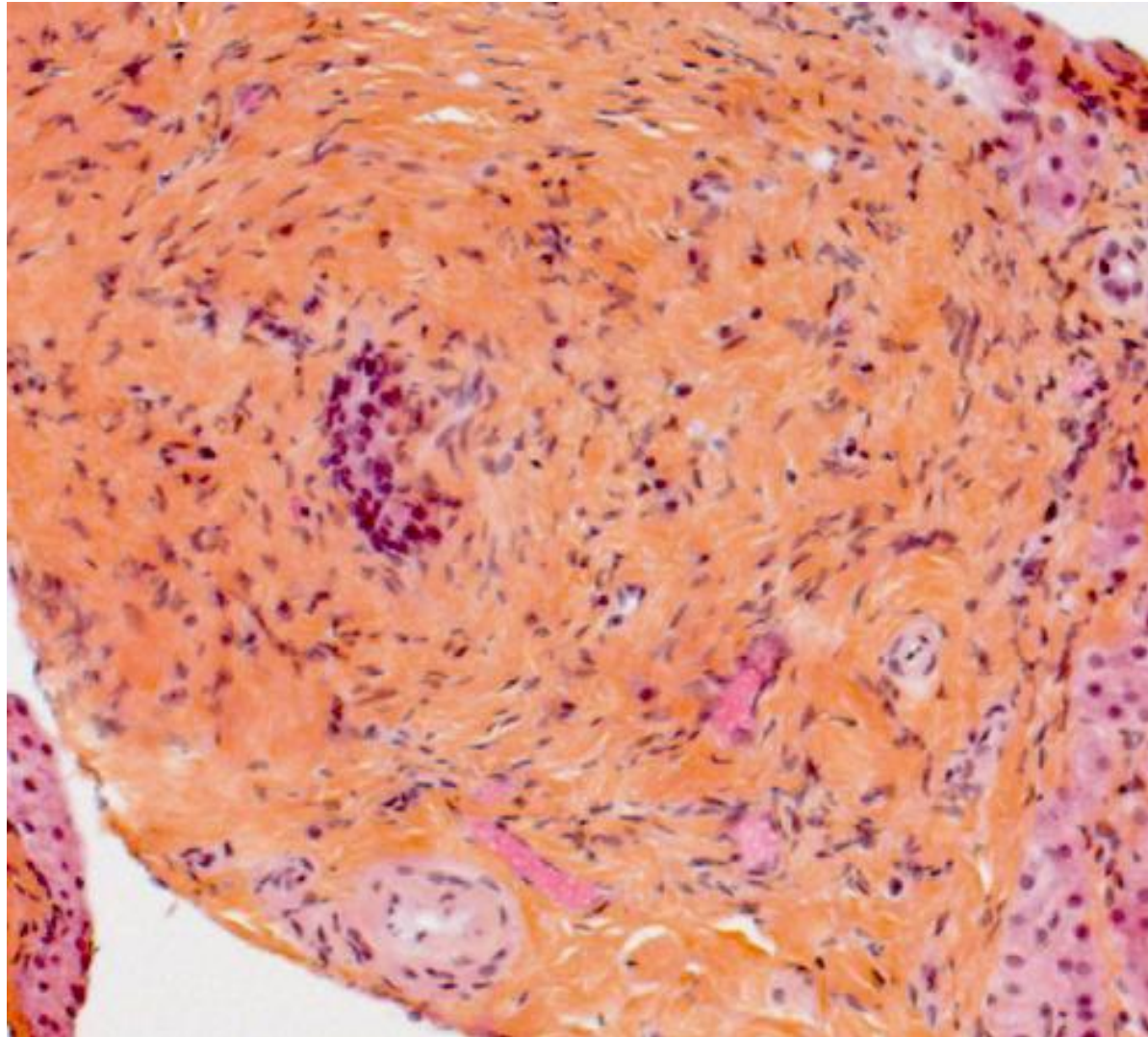
» - Infecciones virales

» - Hepatitis tóxica

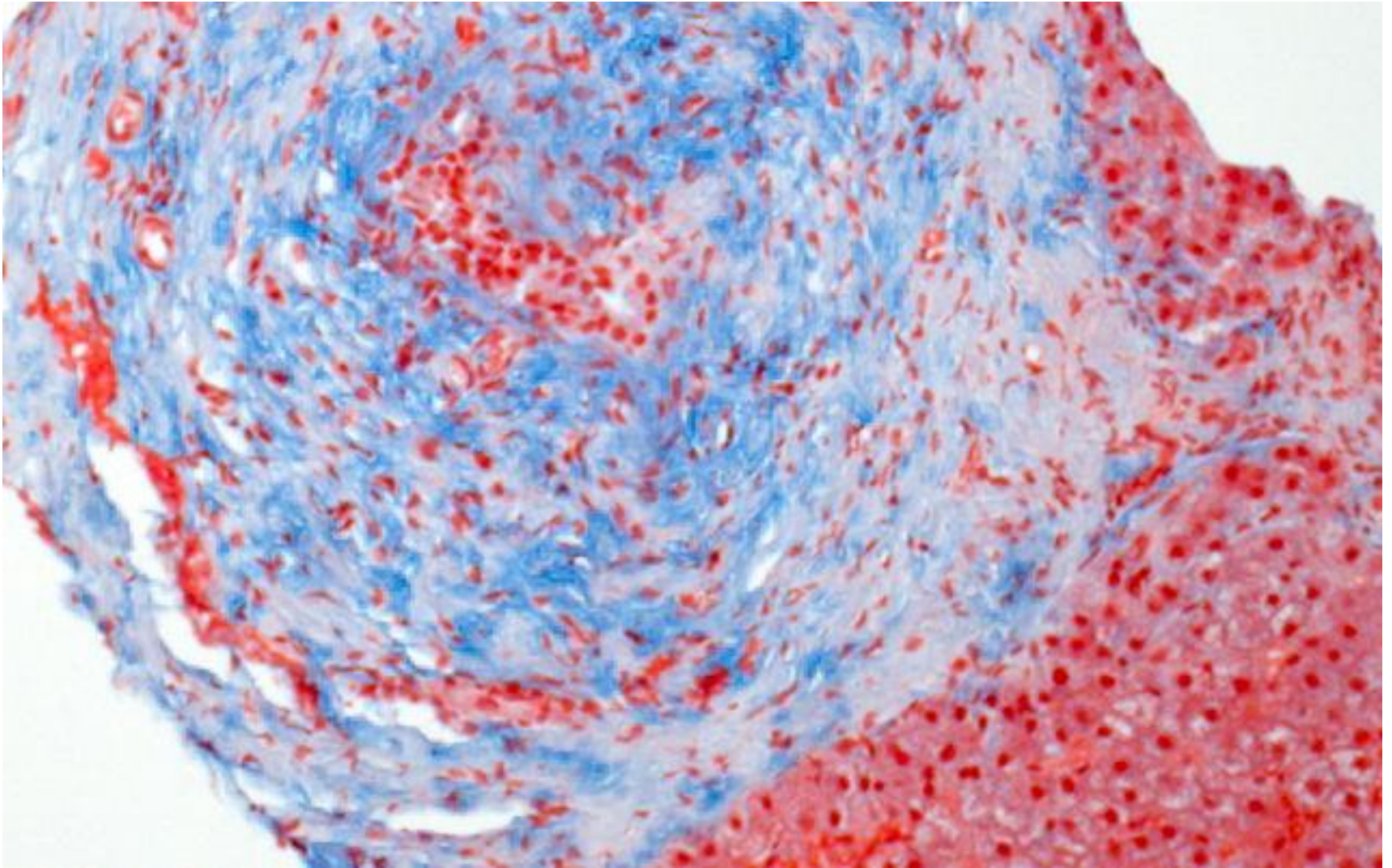
COLANGITIS ESCLEROSANTE



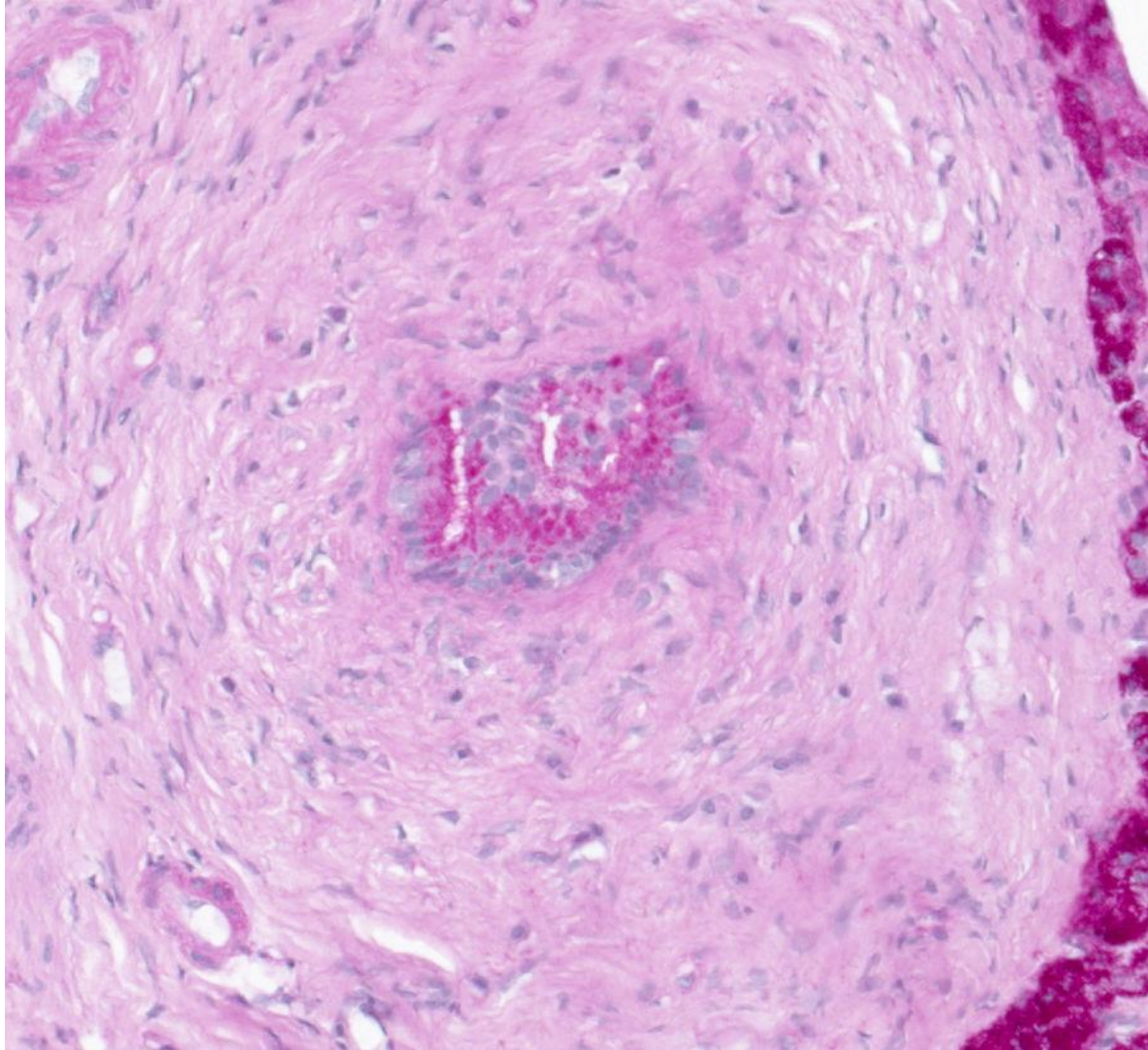
COLANGITIS ESCLEROSANTE



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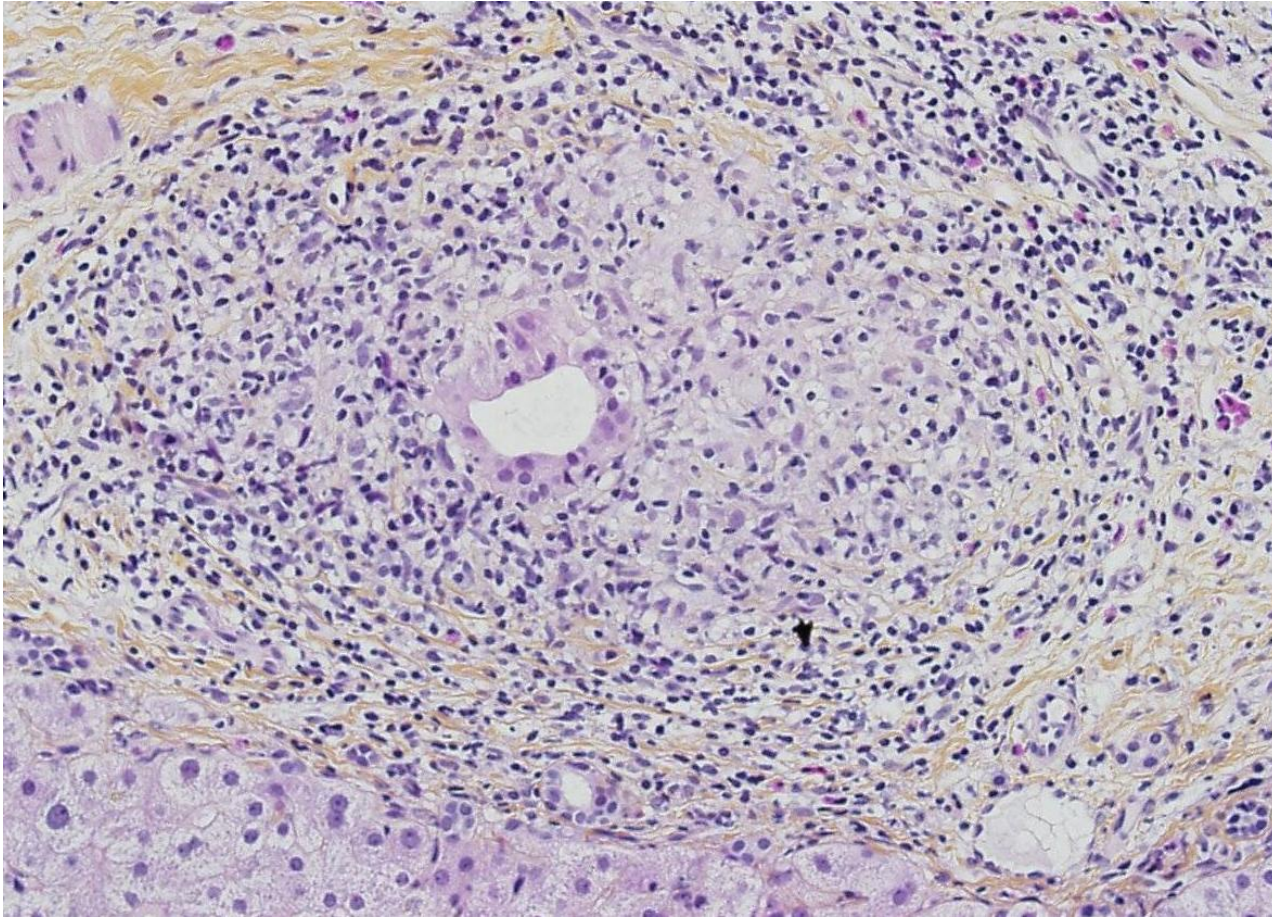


Enfermedades hepáticas mediadas por el sistema inmunitario

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CBP

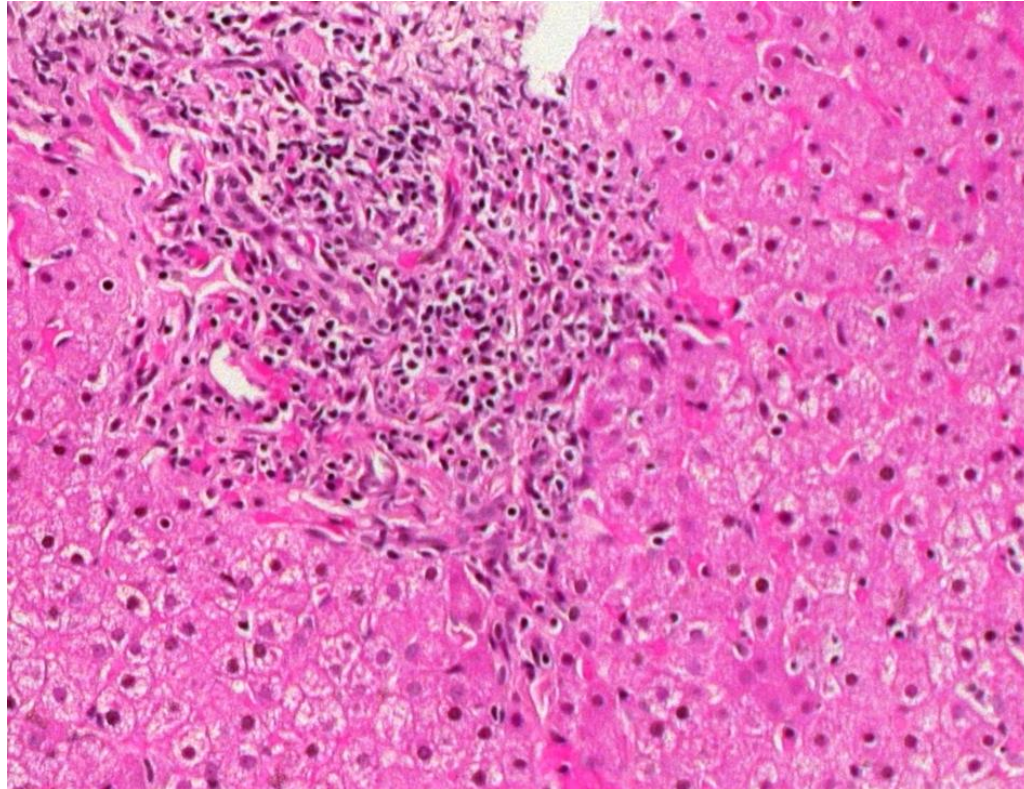


Enfermedades hepáticas mediadas por el sistema inmunitario

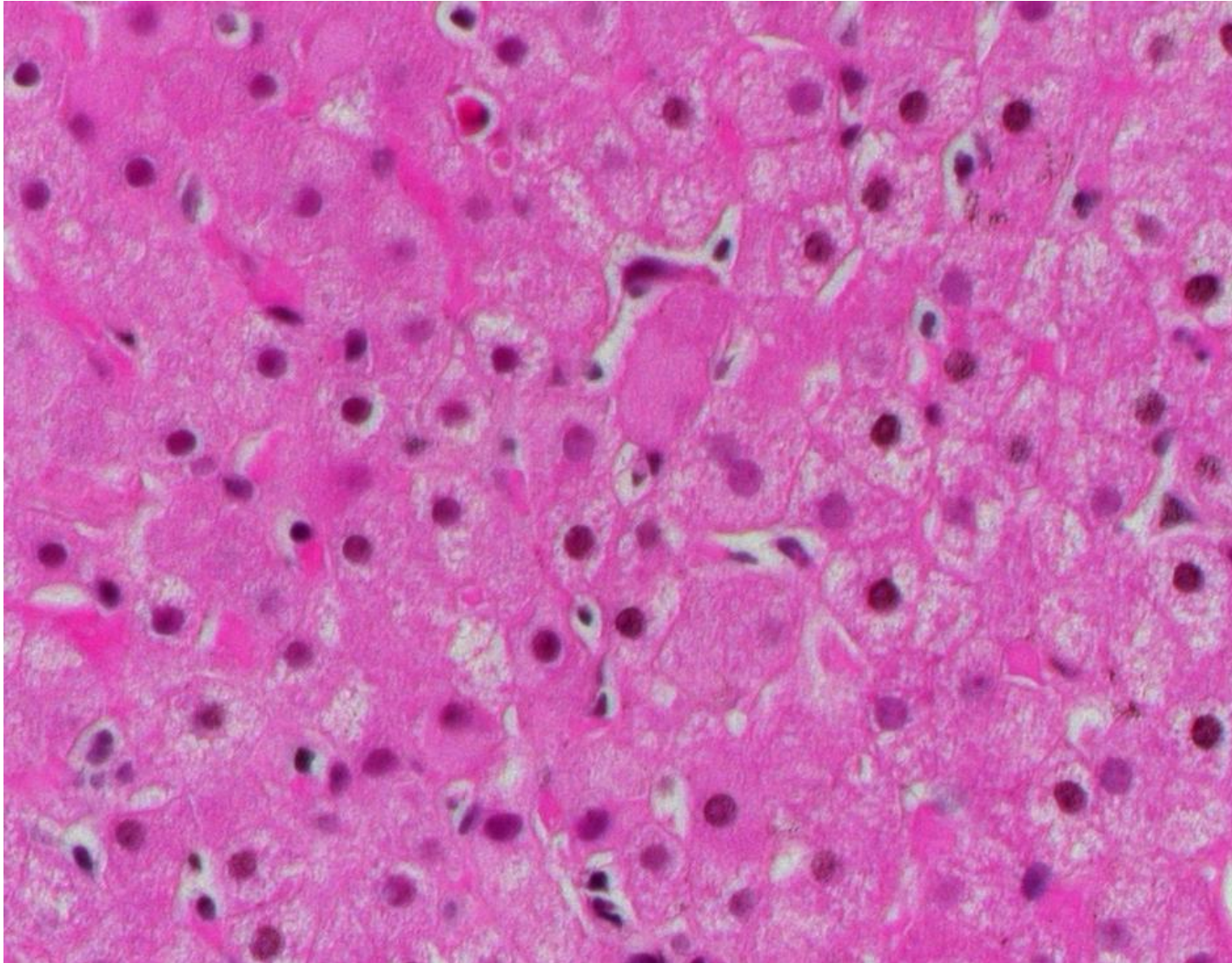
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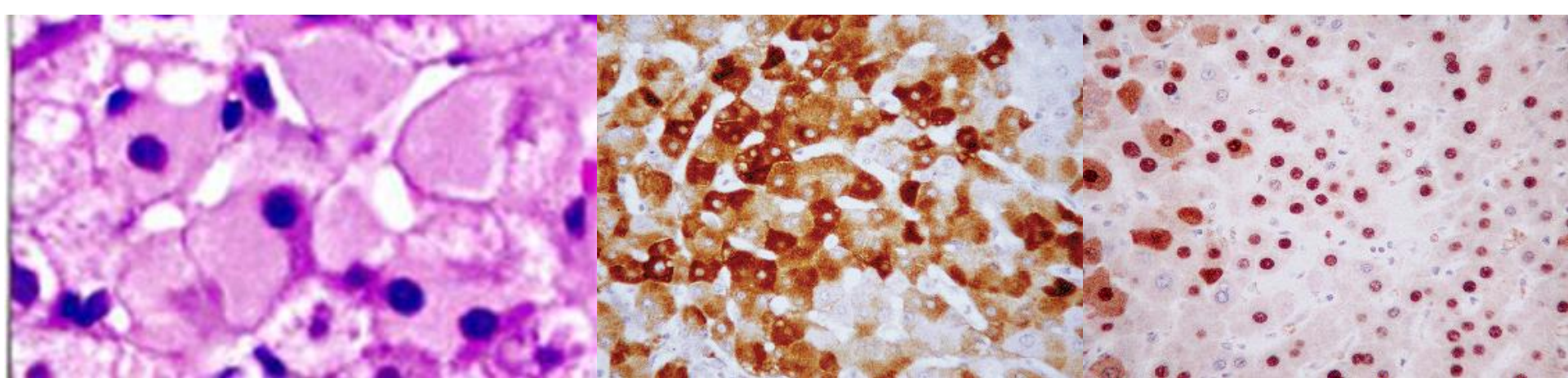
HBV



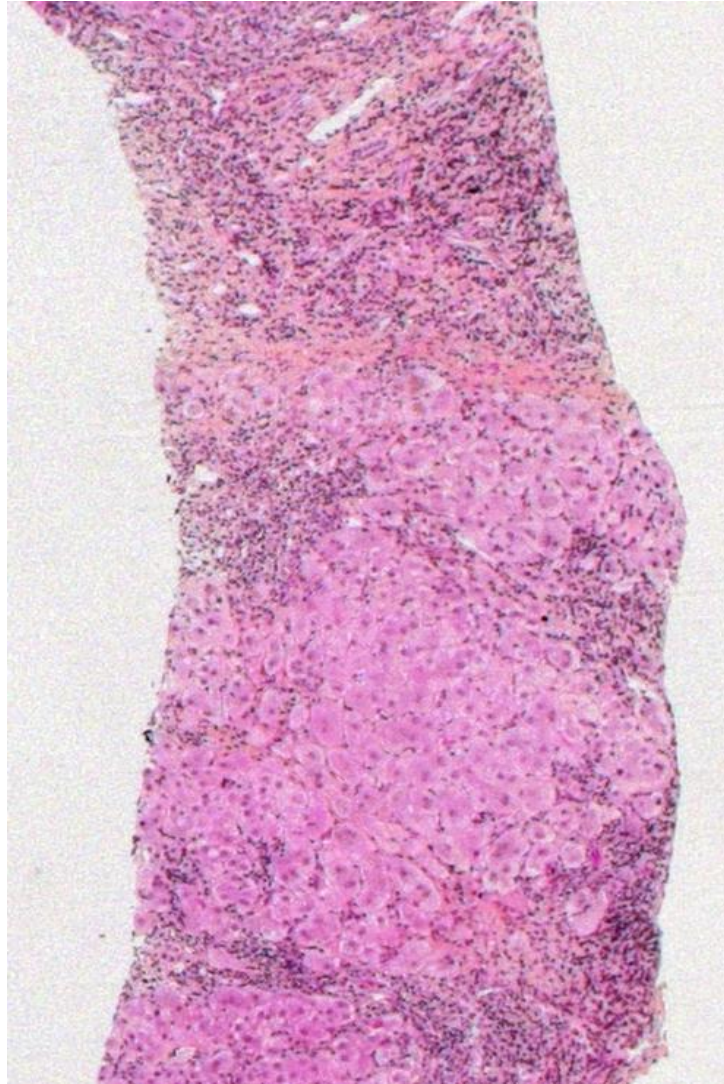
HBV-AgHBs



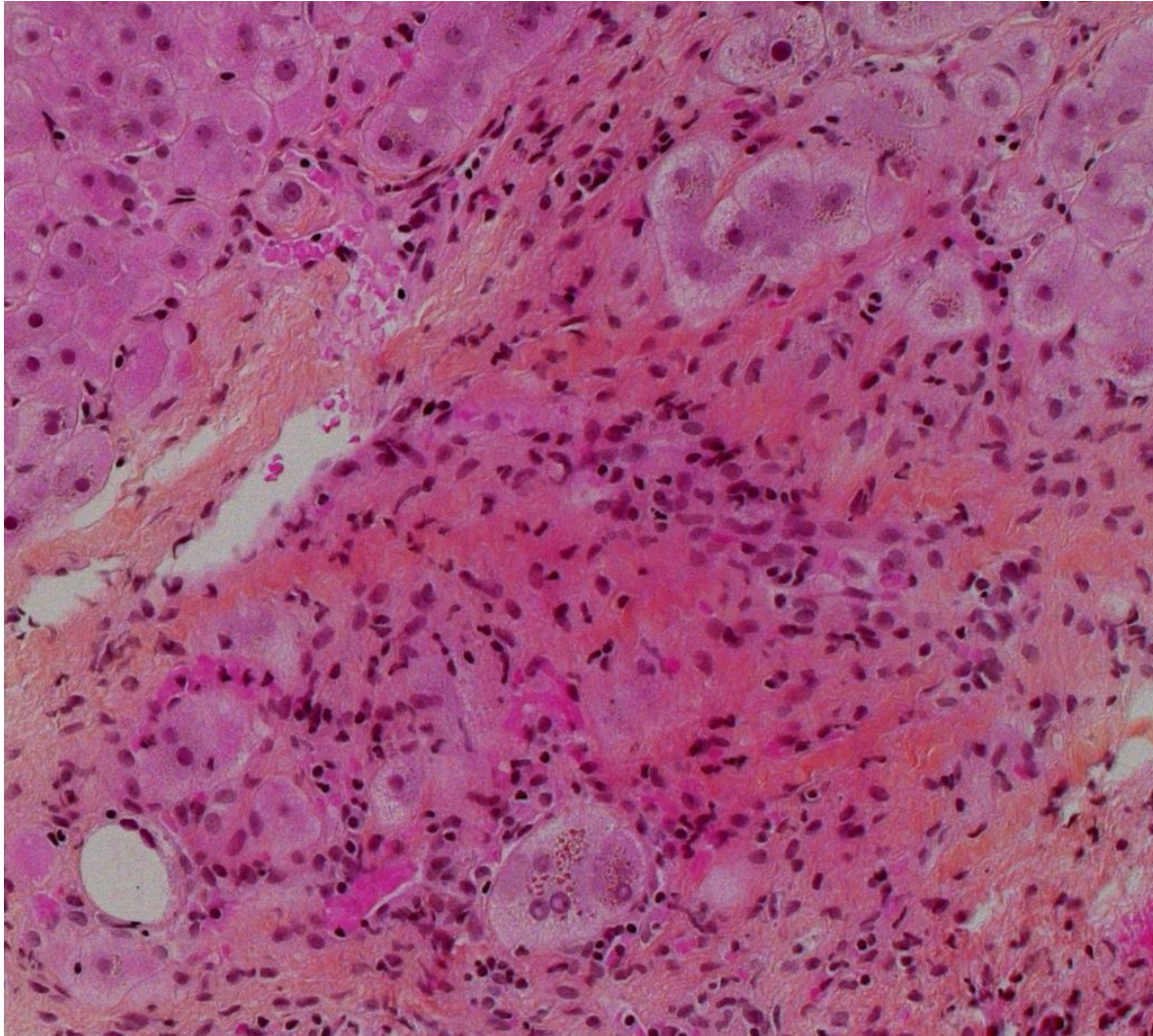
HEPATITIS-VIRUS B



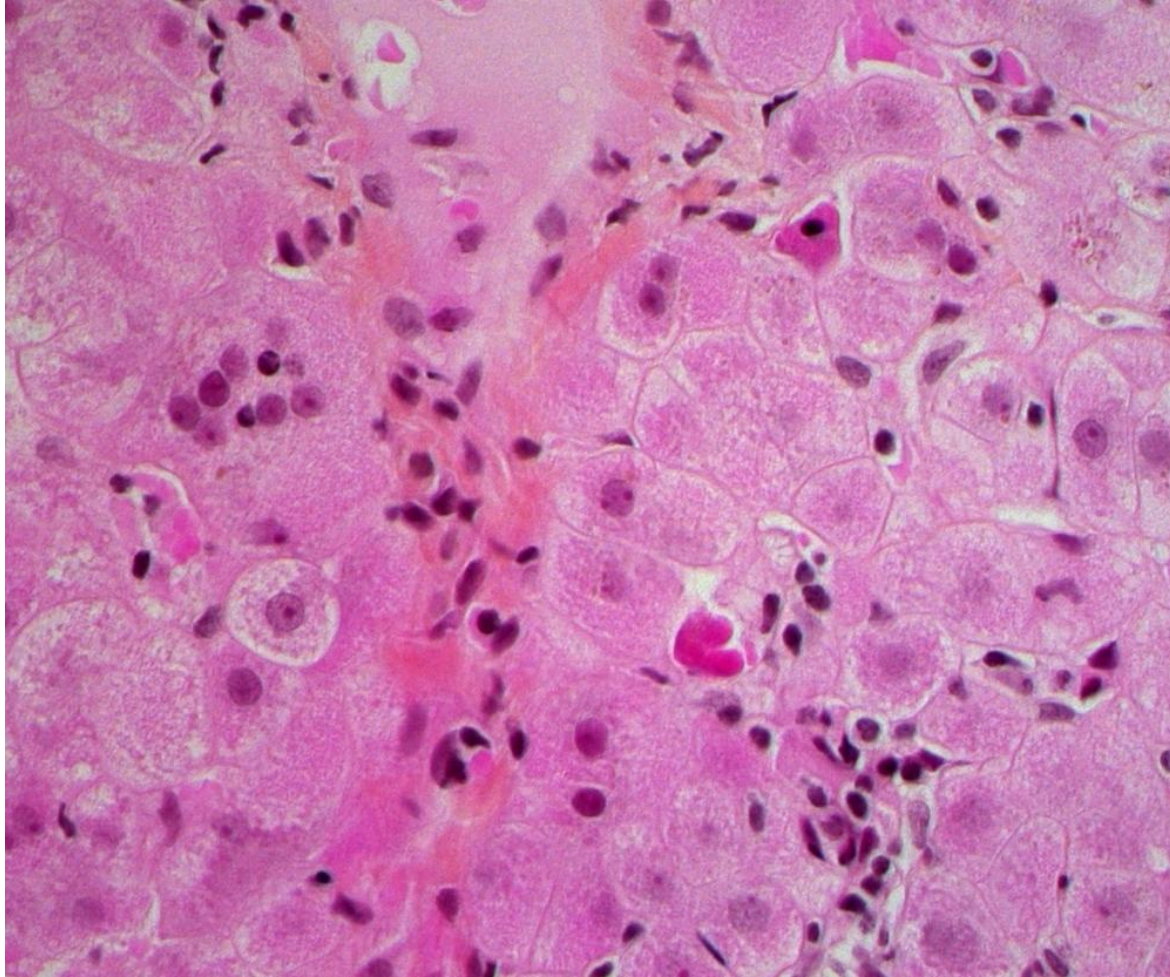
HBV-HDV



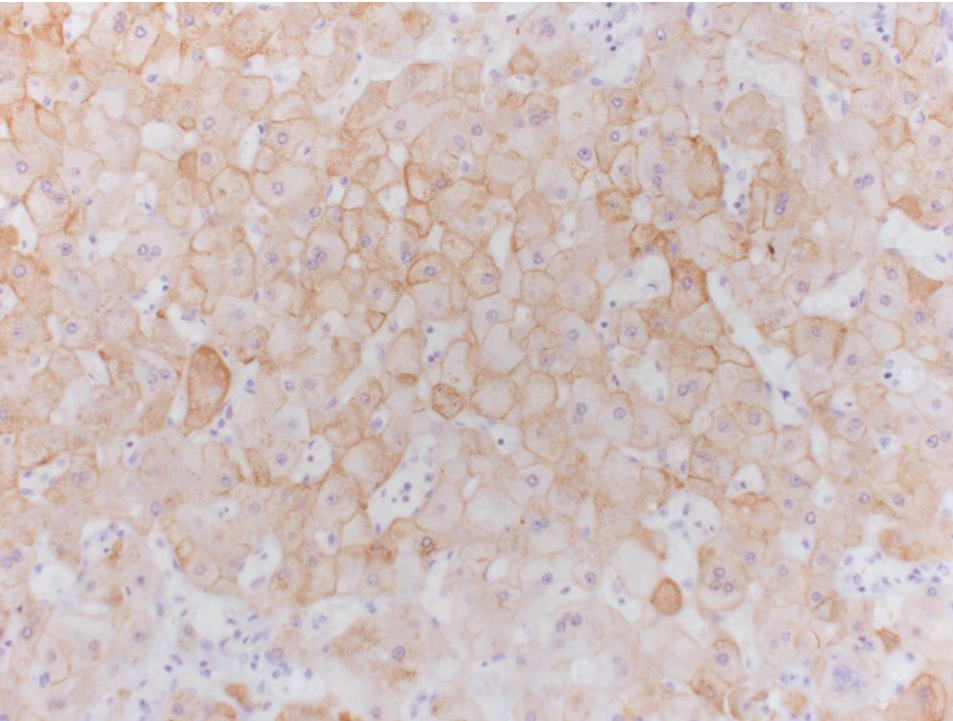
HBV-HDV



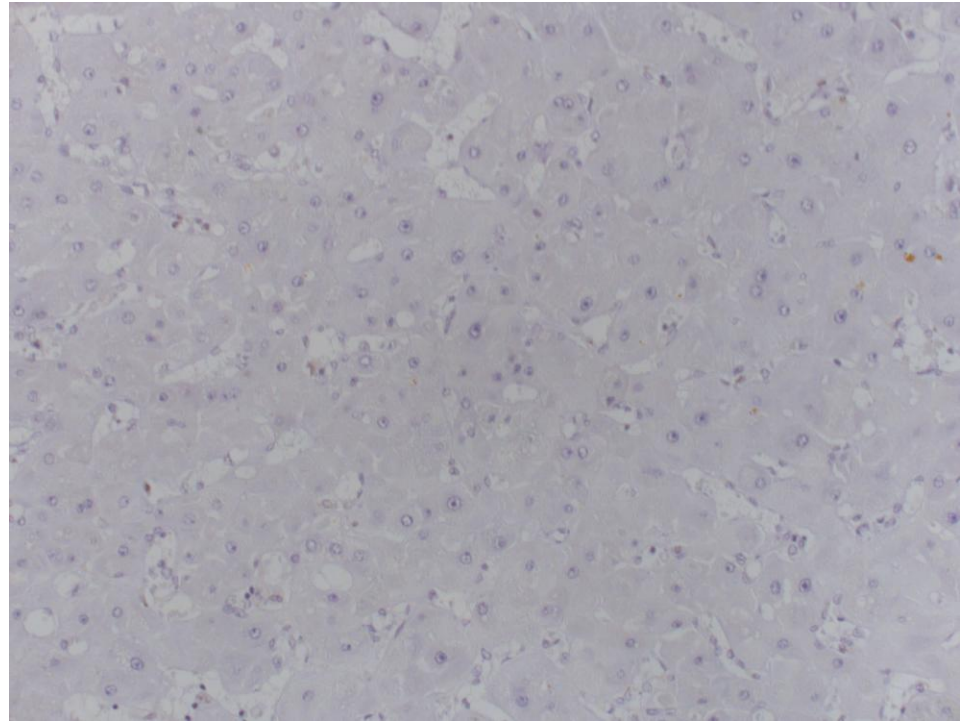
HBV-HDV



HBV-HDV



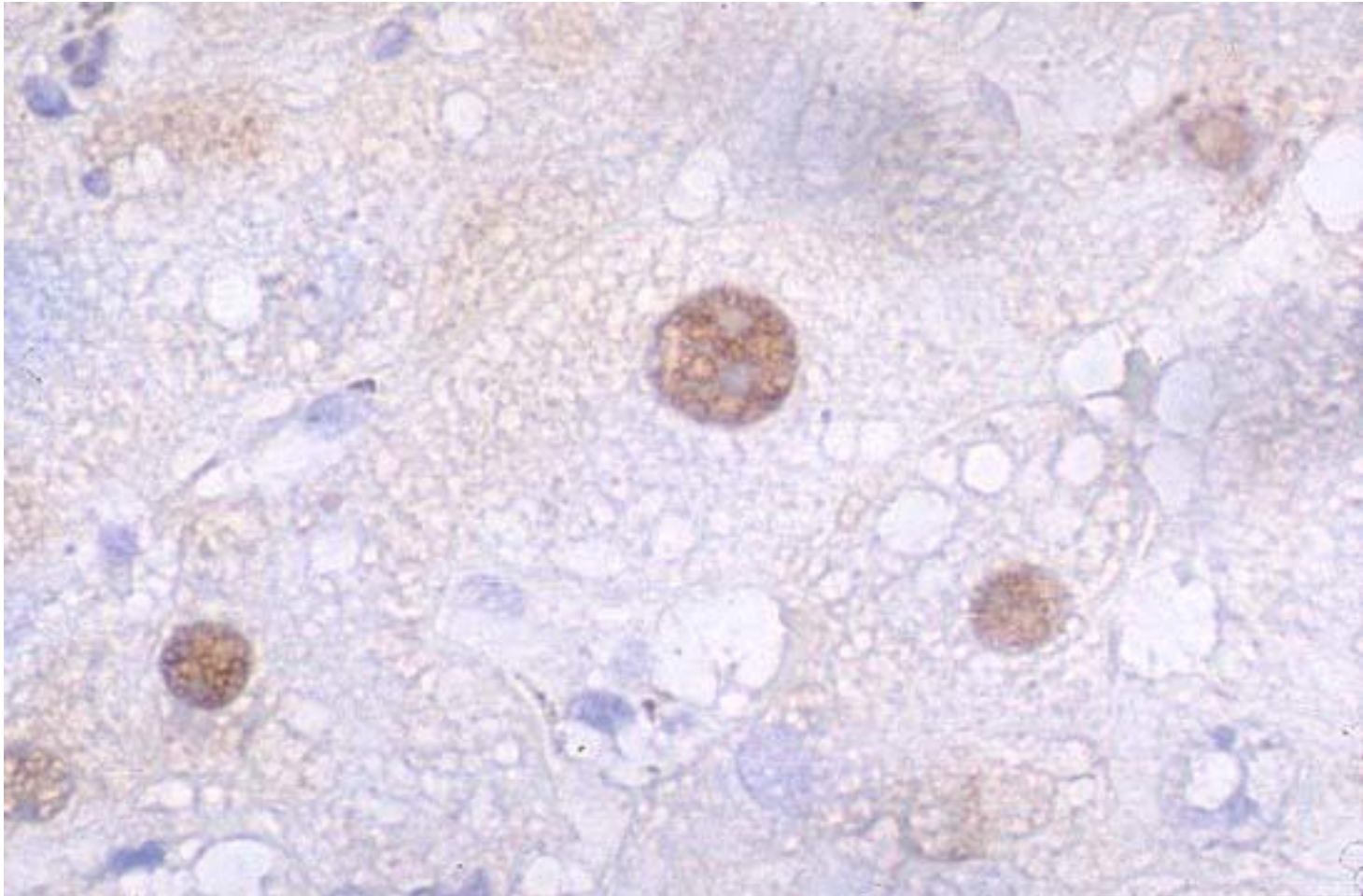
AgHBs



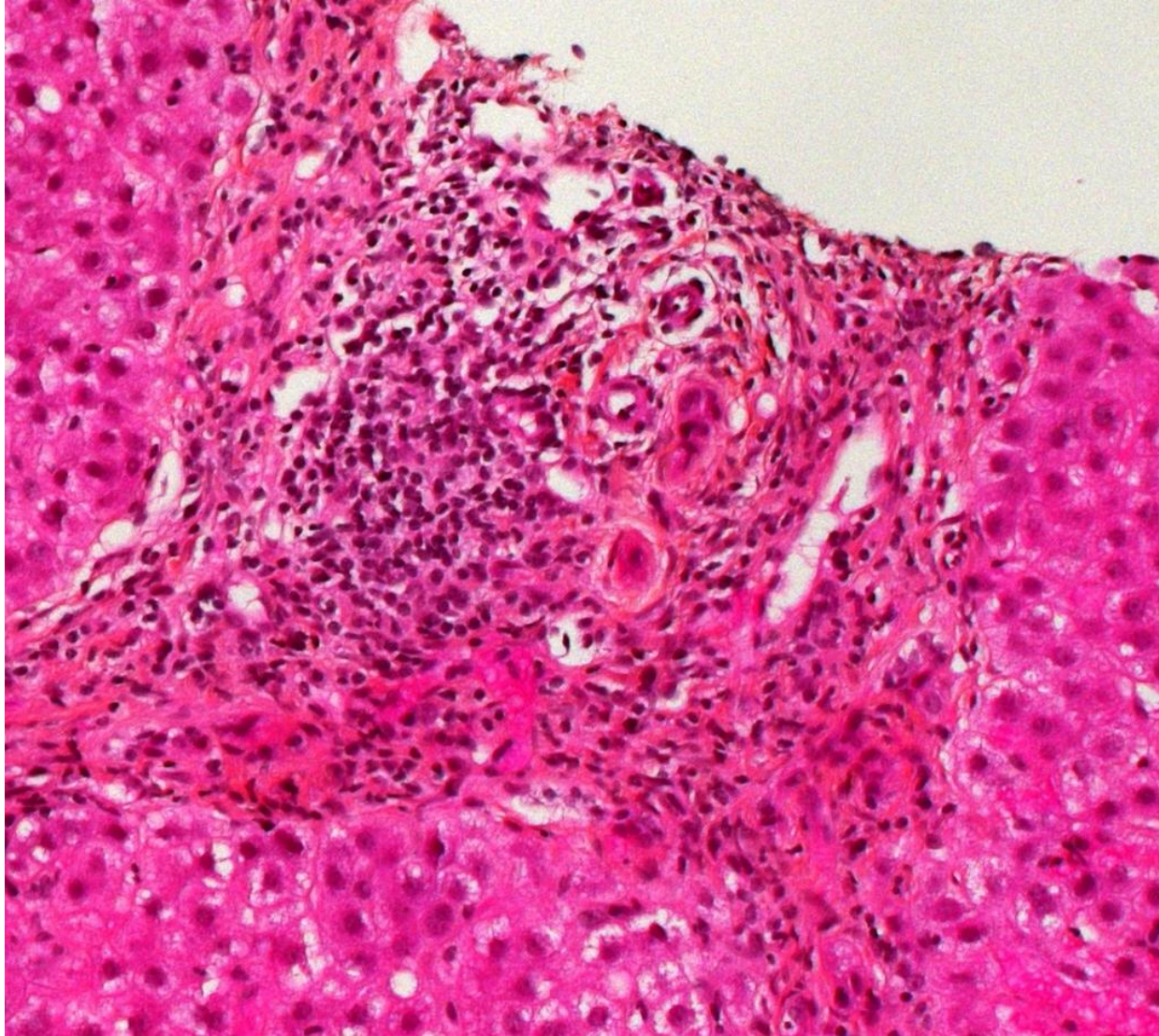
AgHBc

HEPATITIS B CRONICA

Virus delta



HCV

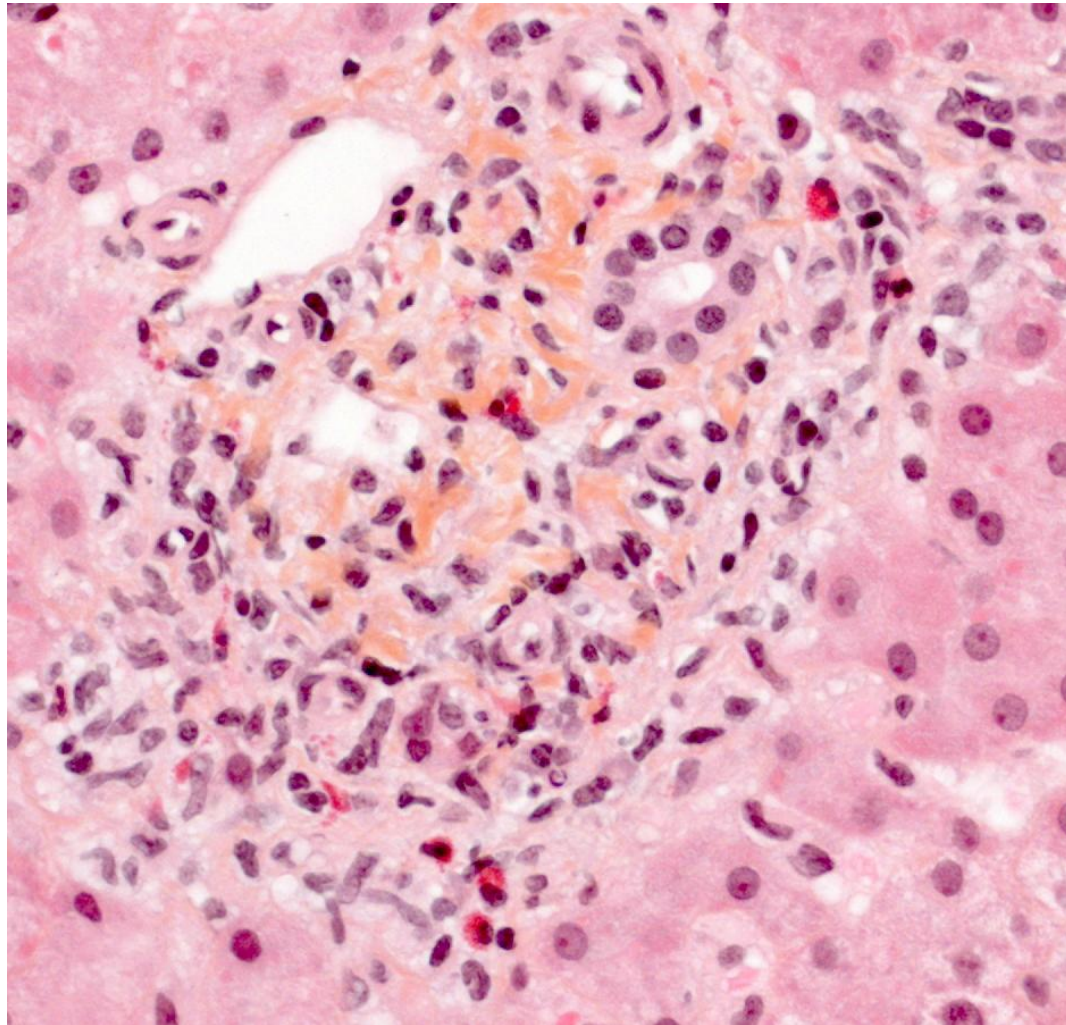


Enfermedades hepáticas mediadas por el sistema inmunitario

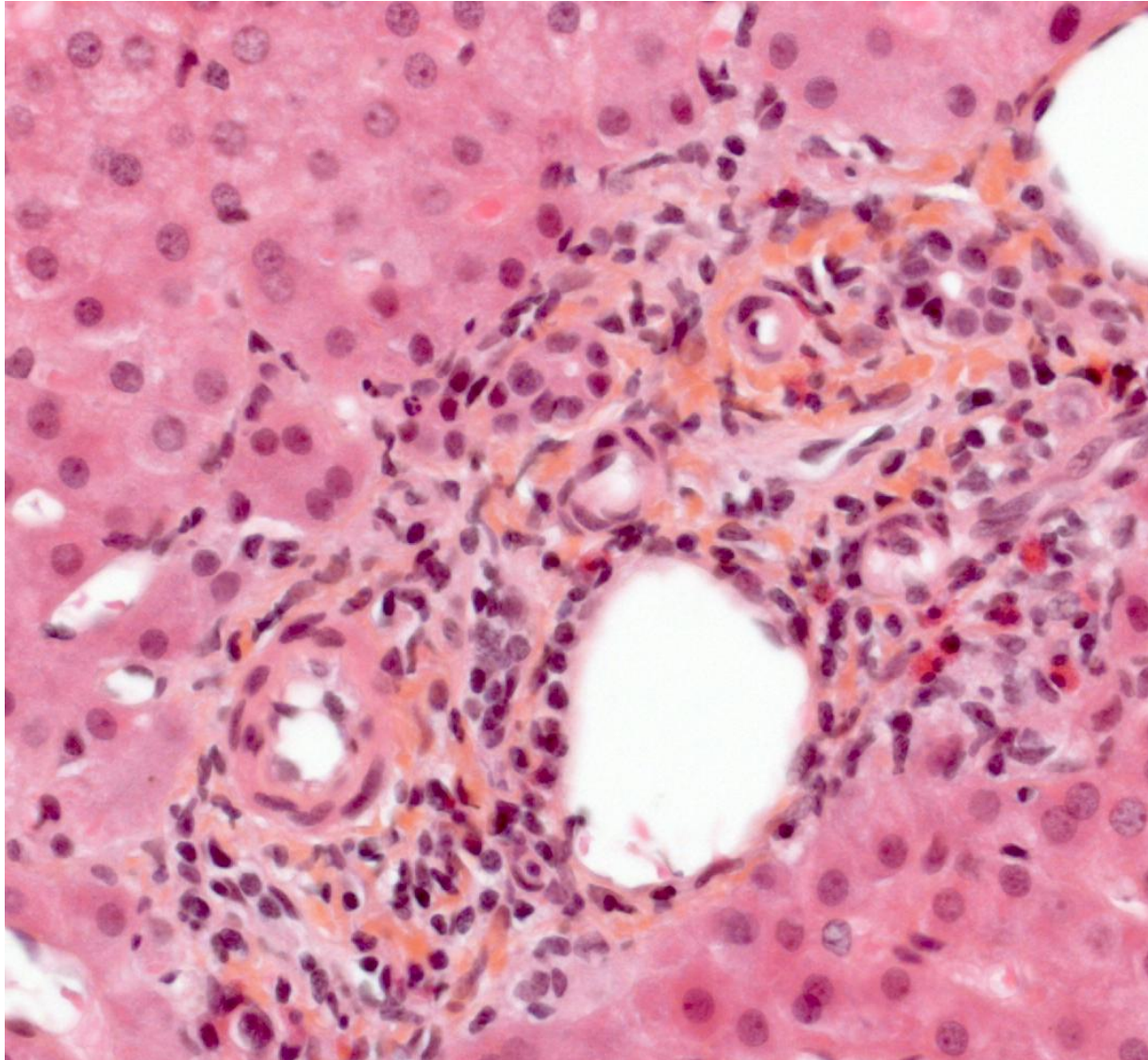
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HEPATITIS INDUCIDA POR DROGAS



HEPATITIS INDUCIDA POR DROGAS

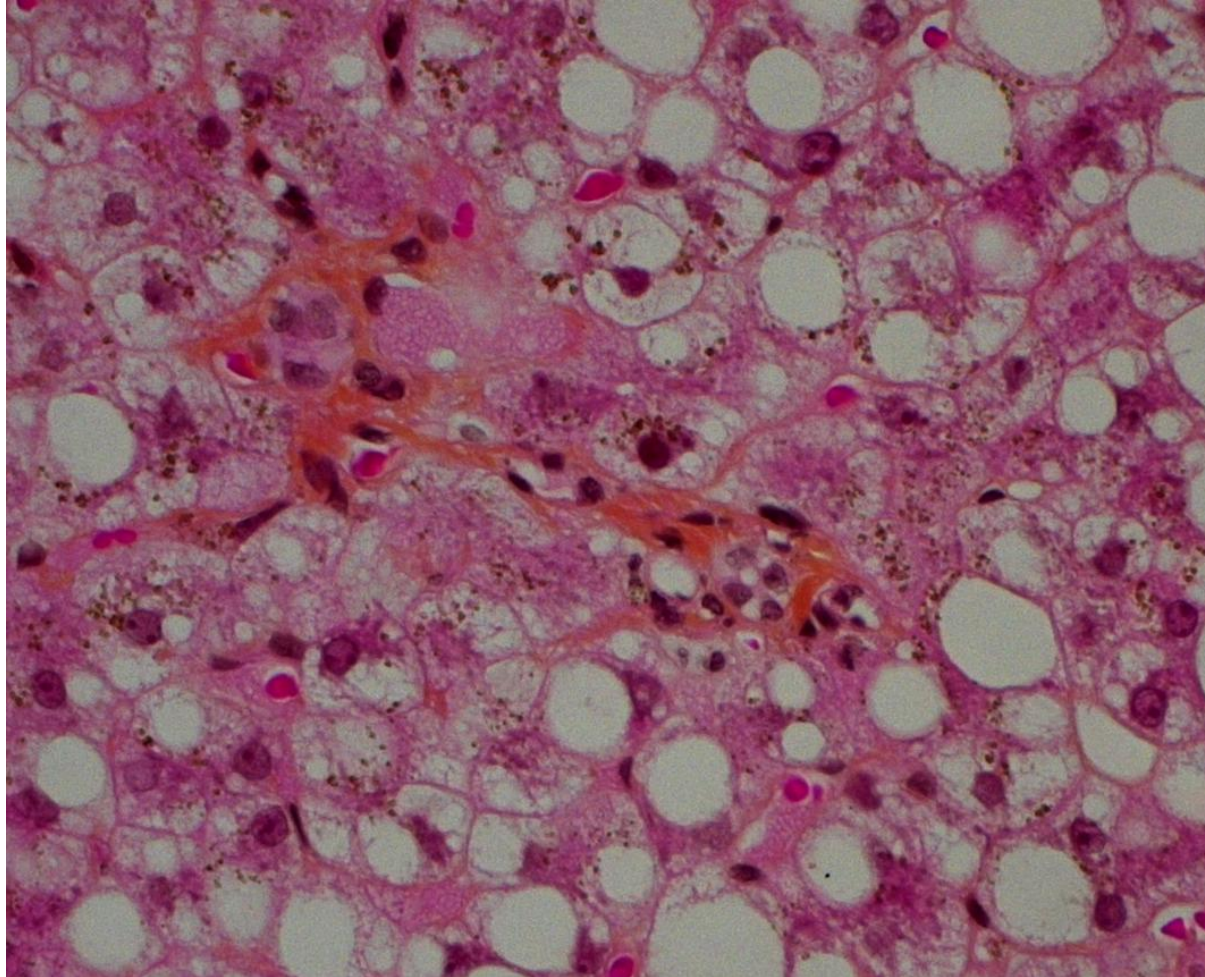


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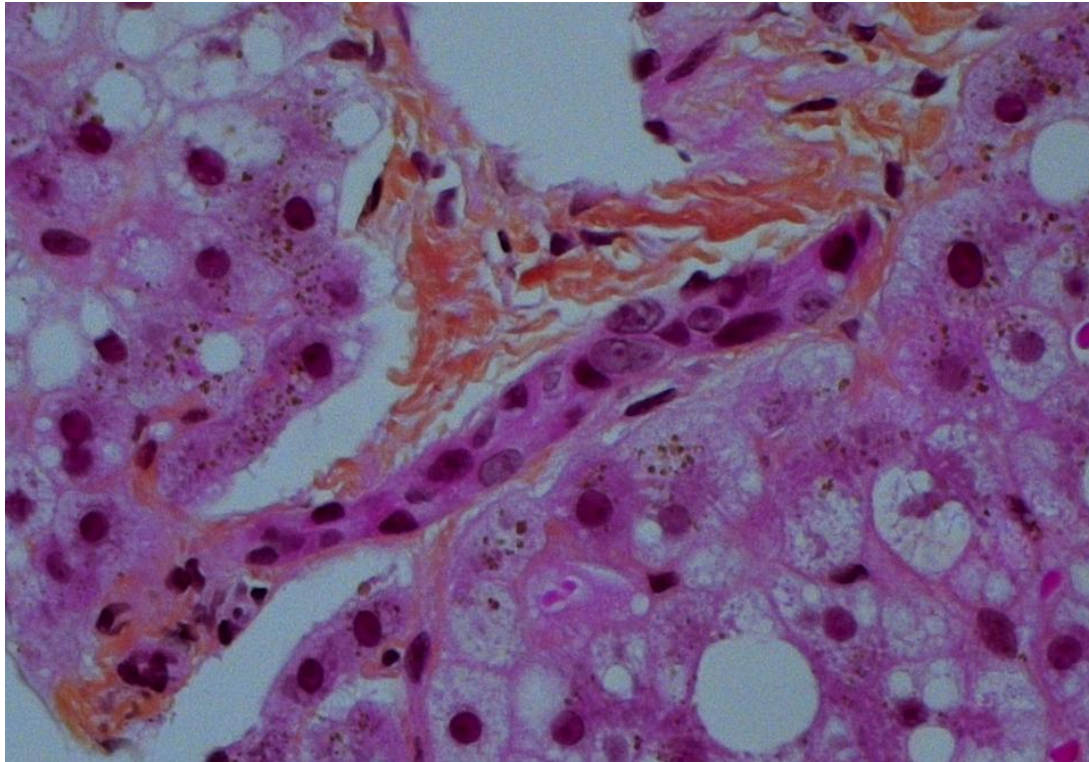
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ICH



ICH

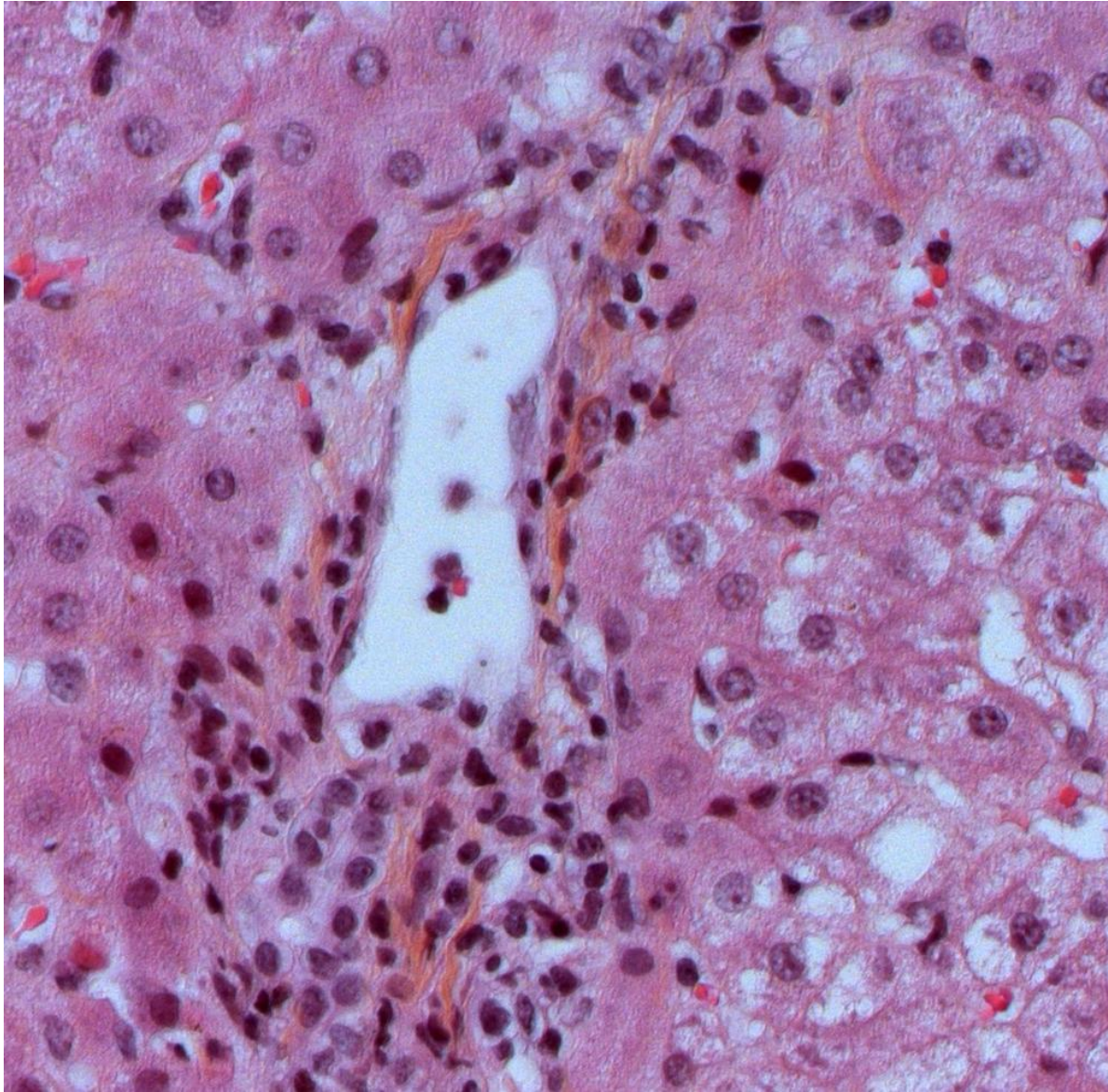


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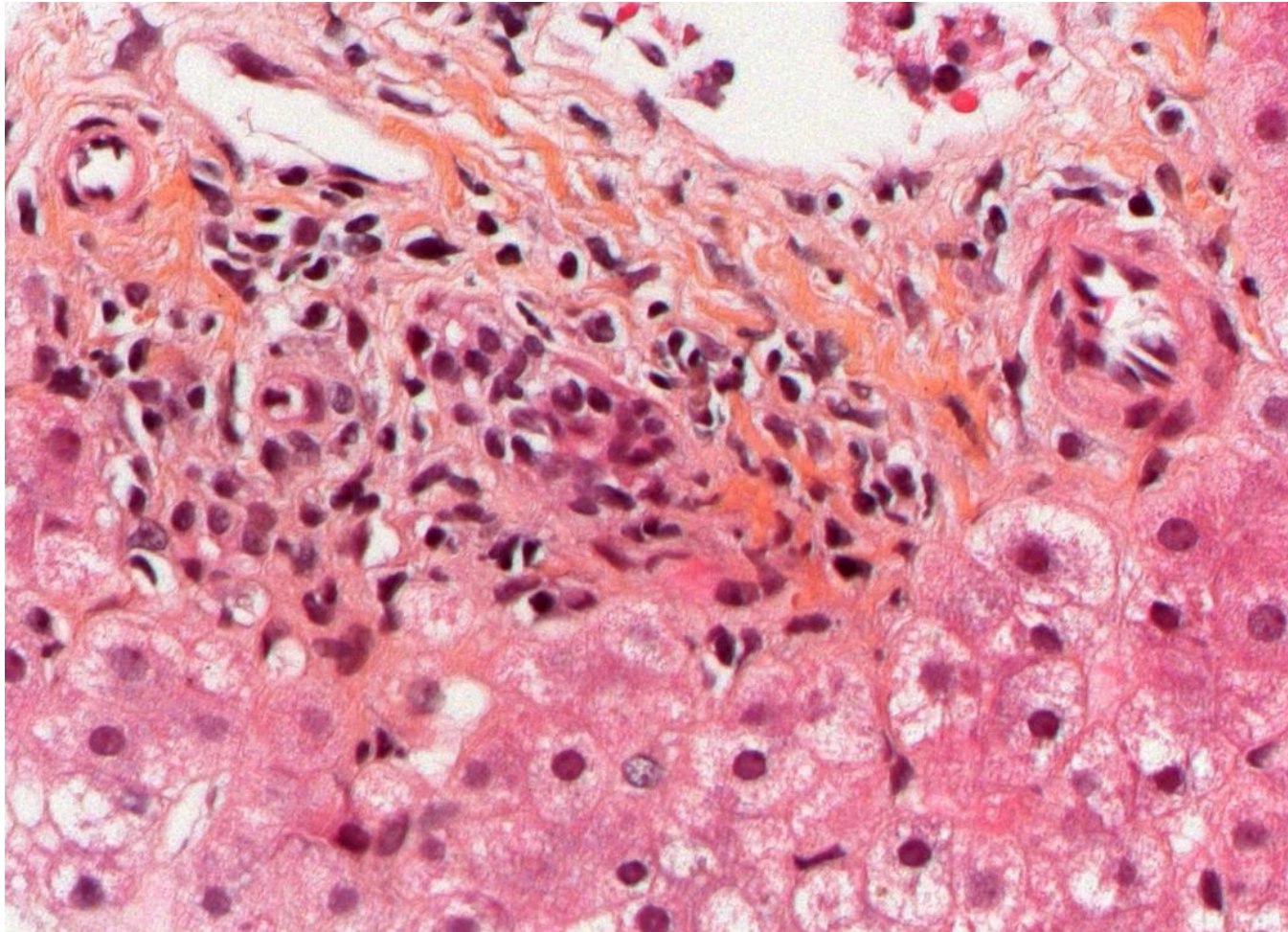
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RECHAZO-ENDOTELIALITIS



RECHAZO-CANAL BILIAR

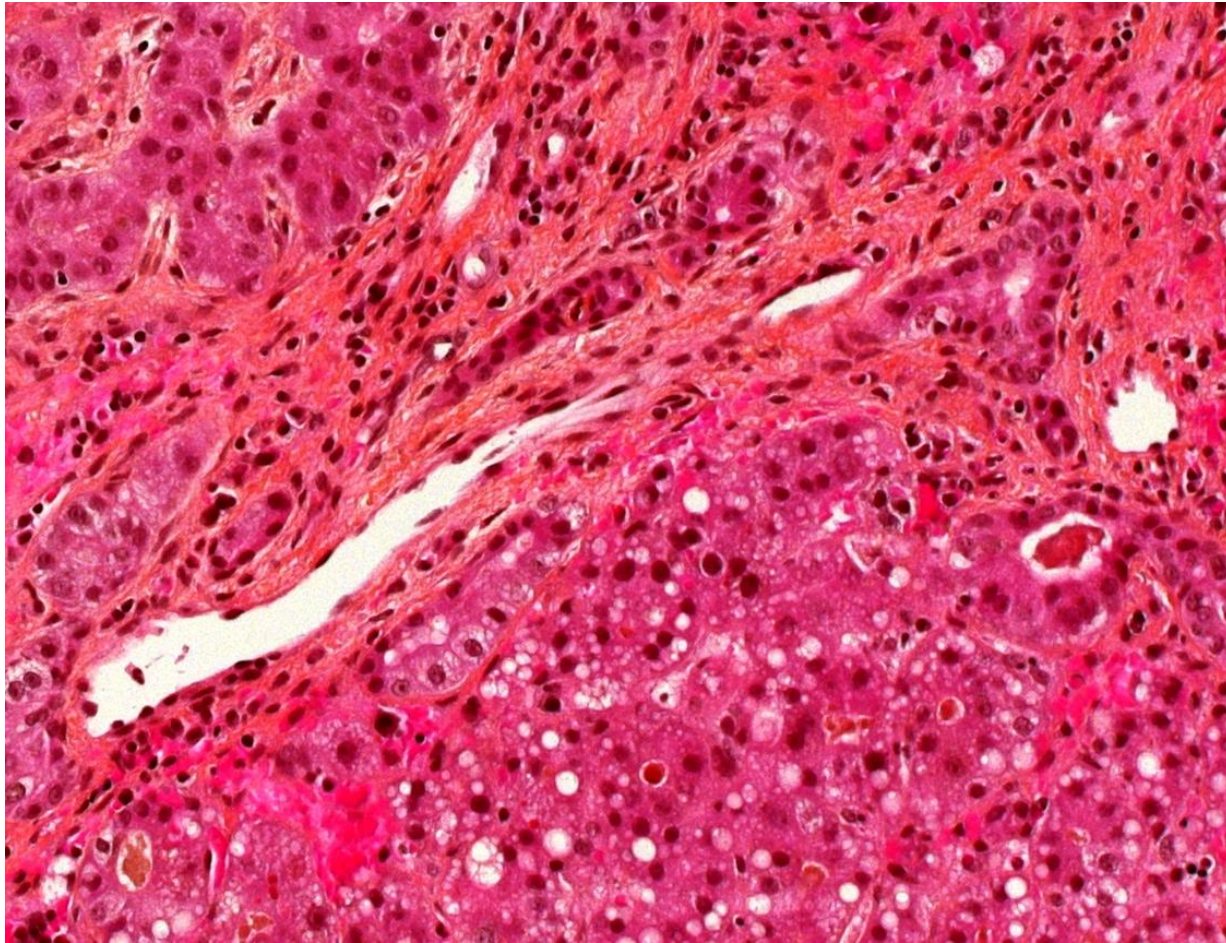


Enfermedades hepáticas mediadas por el sistema inmunitario

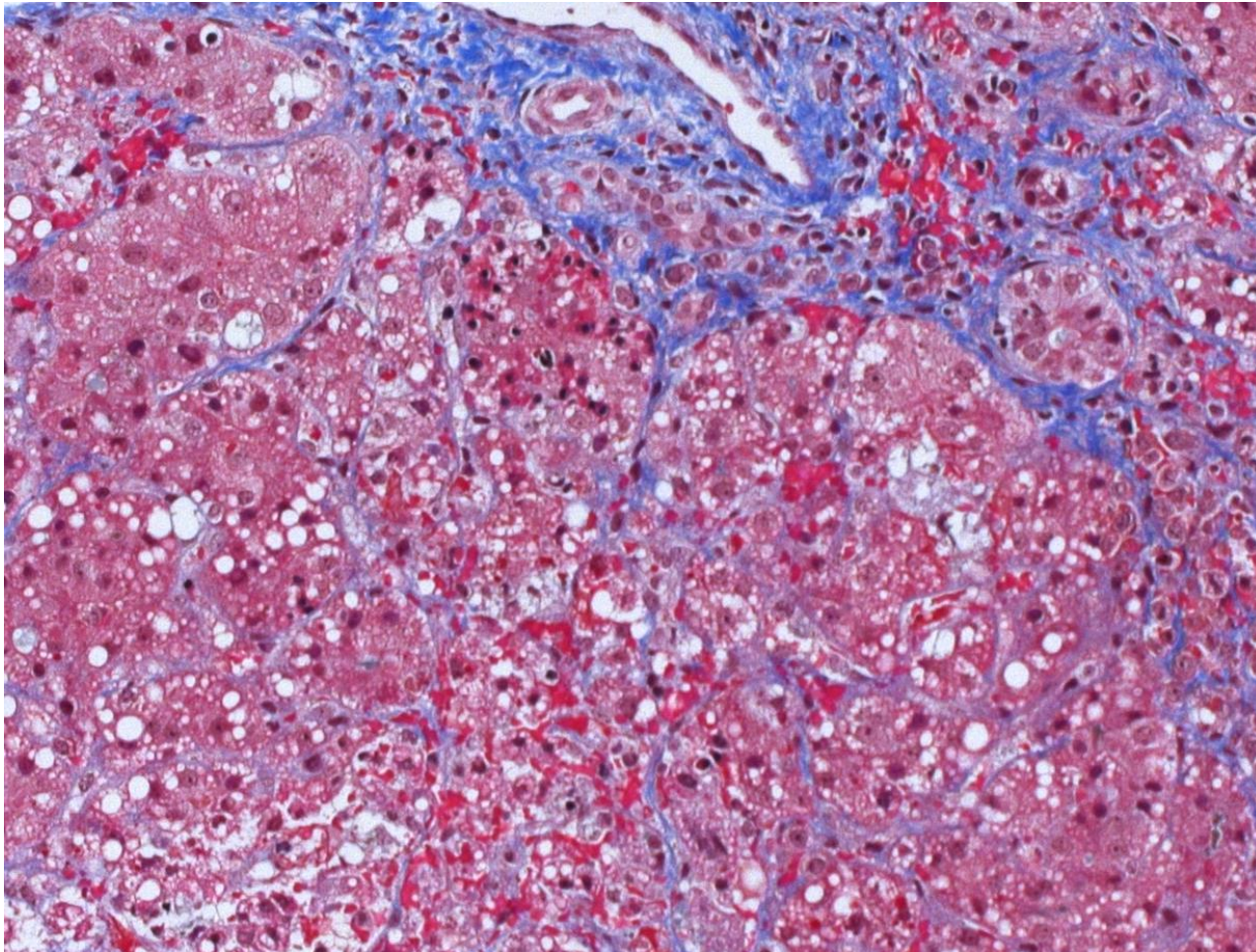
2) Enfermedades provocadas por anticuerpos:

- - Hepatitis fetal aloinmune
- - Hepatitis a células gigantes con anemia hemolítica autoinmune
- - Rechazo mediado por anti-HLA

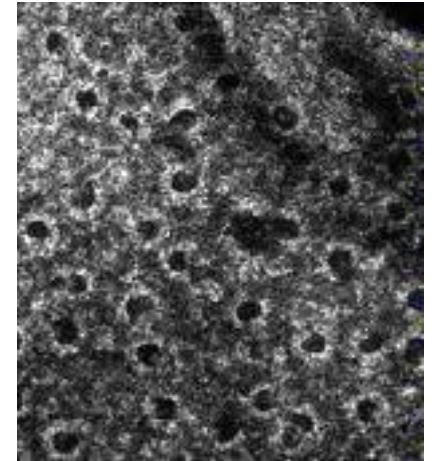
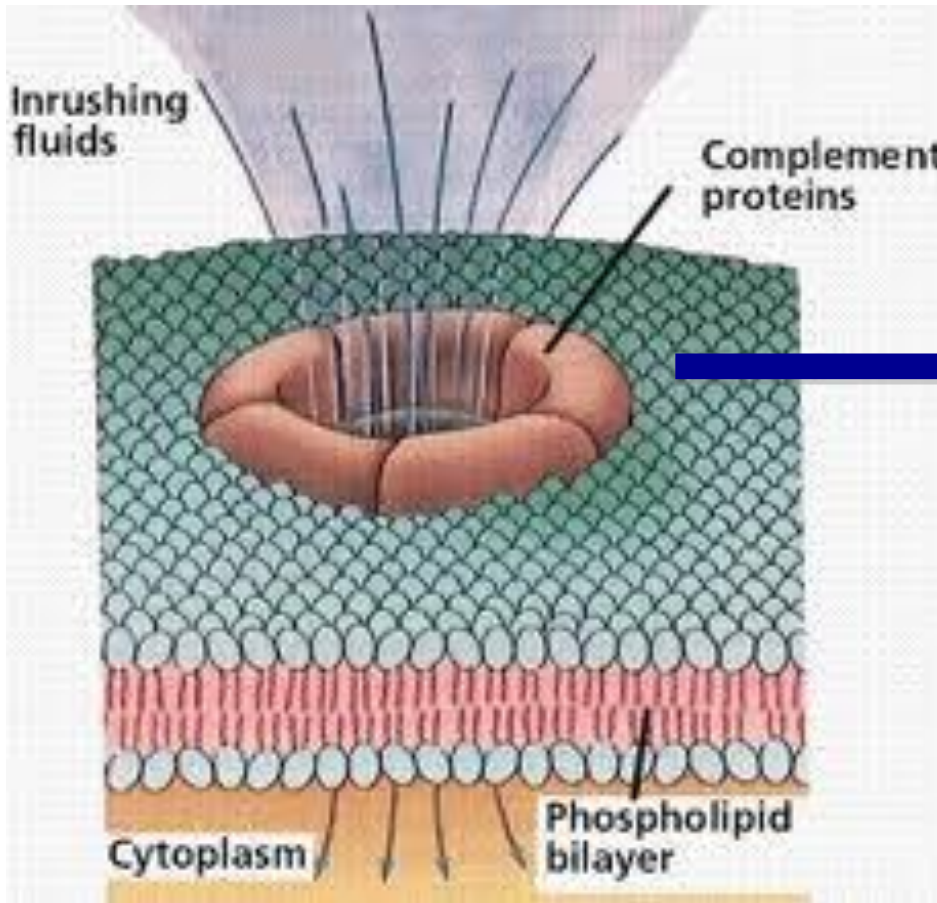
Hepatitis fetal aloinmune



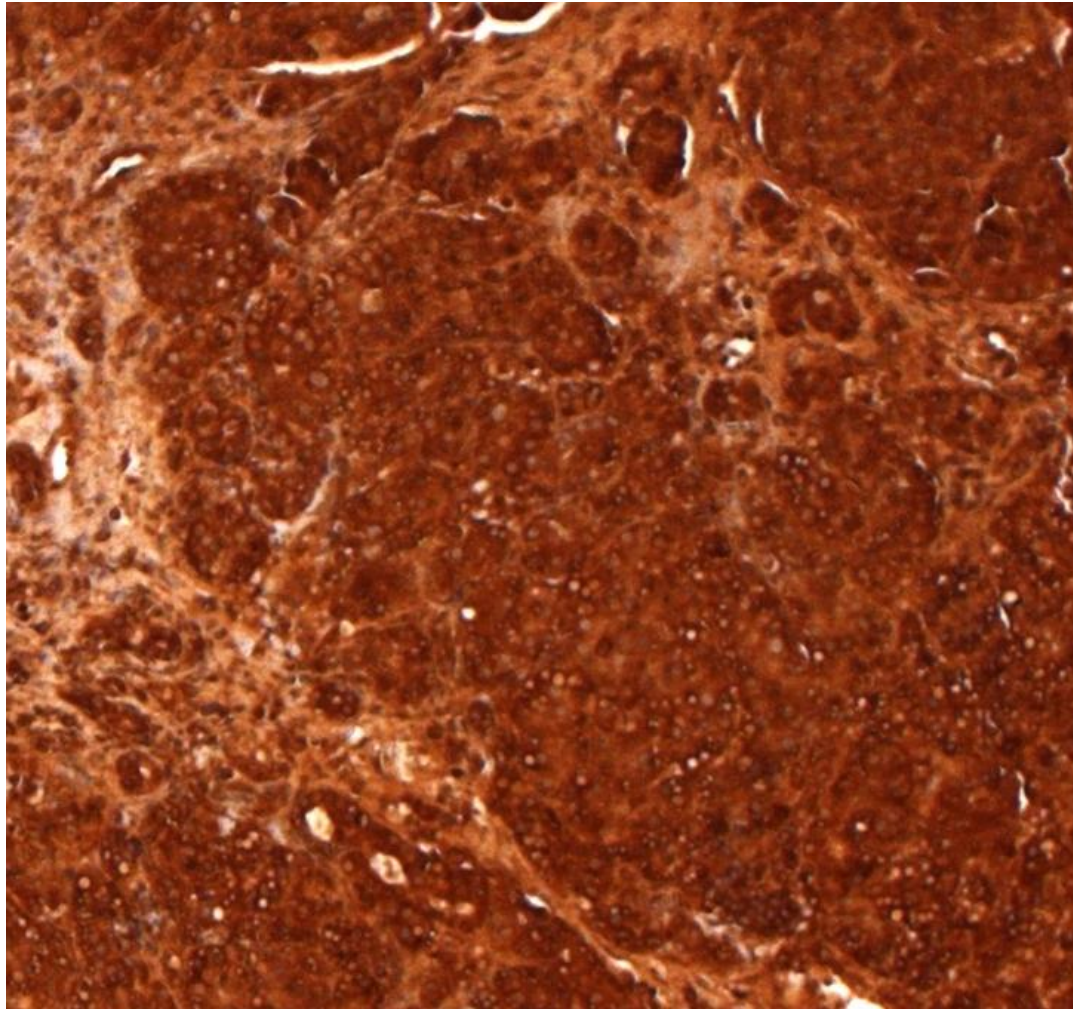
Hepatitis fetal aloinmune



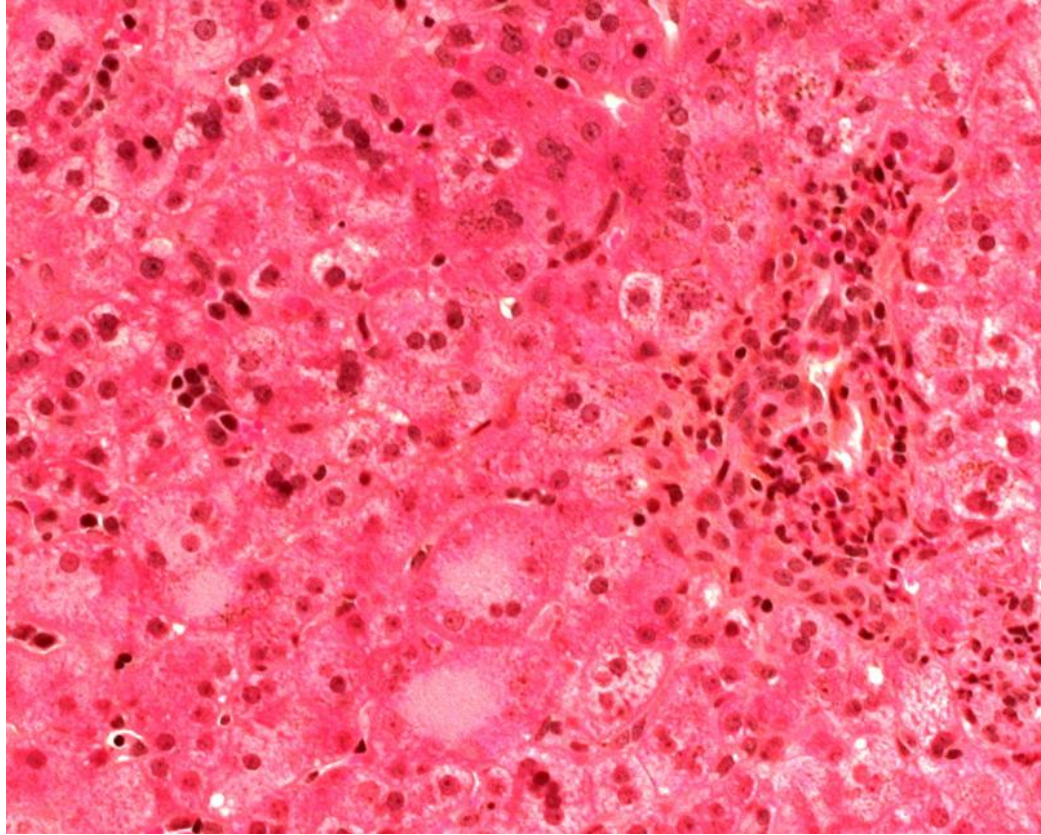
Membrane attack complex (MAC)



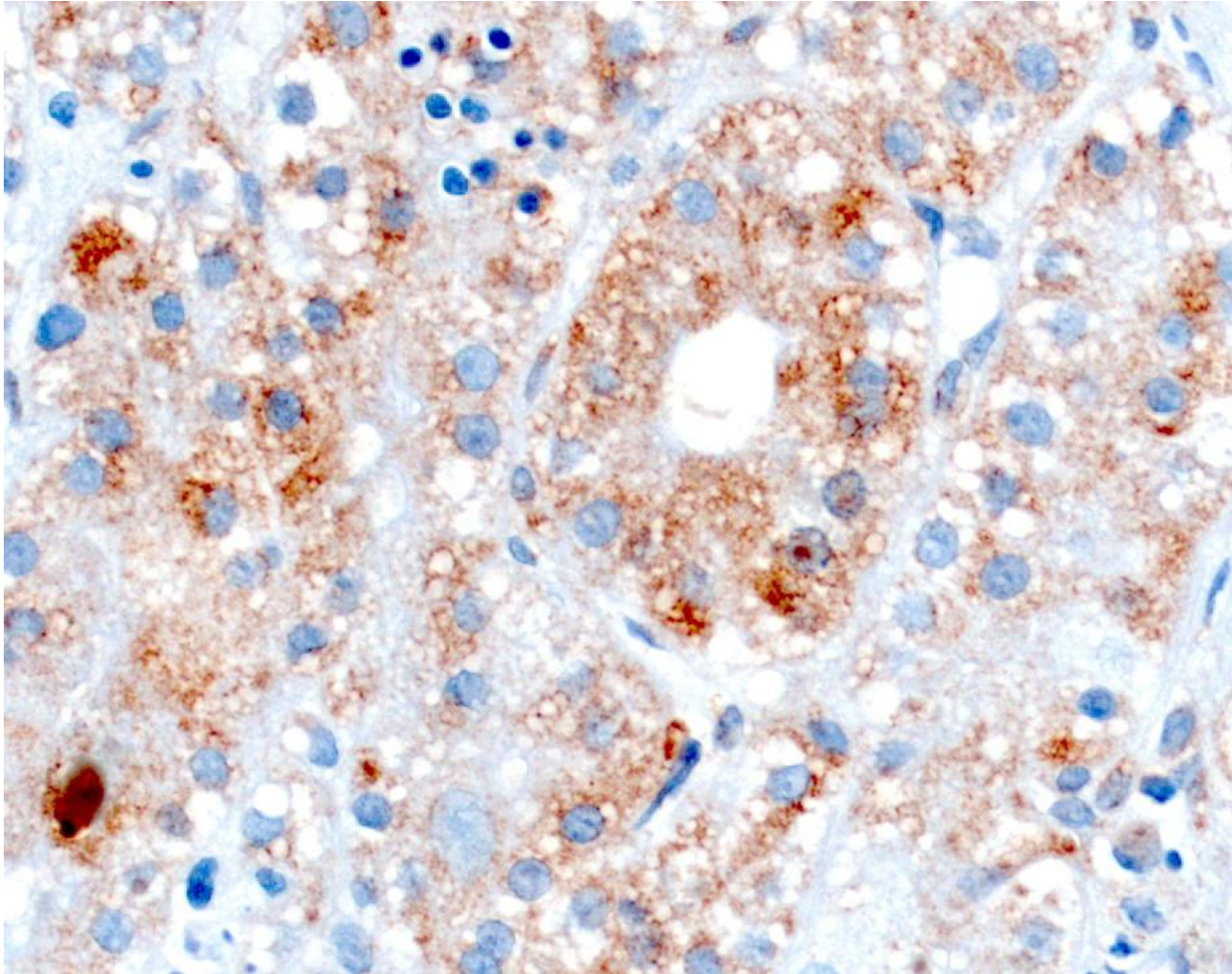
Inmuno-histo



HCG-AHA



HCG-AHA CAM+



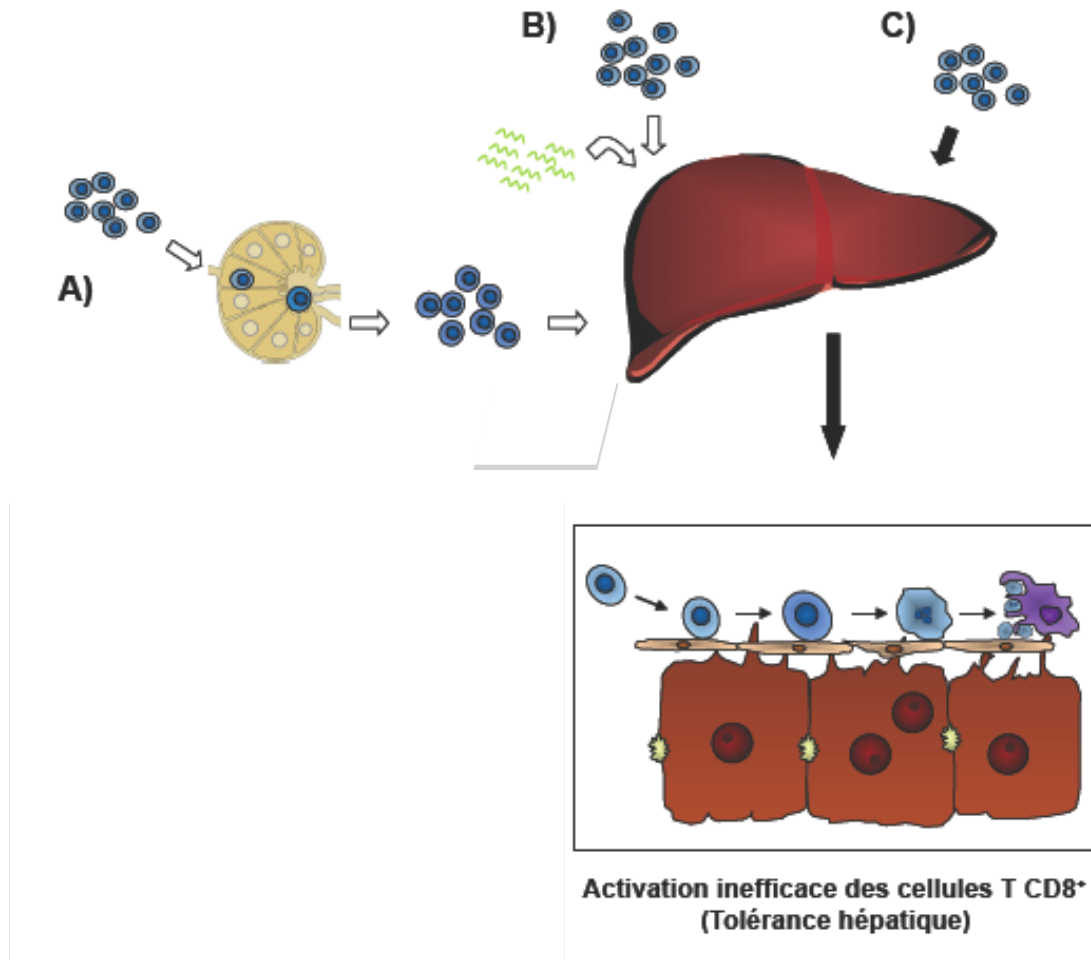
Enfermedades hepáticas mediadas por el sistema inmunitario

3) Inflamación responsable de muerte celular:

- Inflamación de células T no específica: « bystander hepatitis ».

(ejemplos: infección por EBV, enf. Inflamatoria del intestino, etc)

« Linfocitos son atraídos al hígado »



Mecanismos de migración & inflamación

Adhesion molecules

- Vap-1
- ICAM-1
- VCAM-1
- E-Selectin

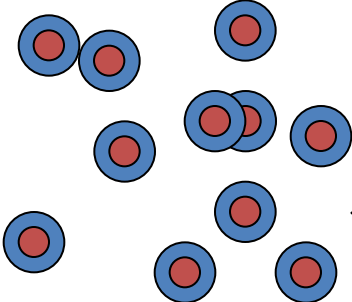


Chemokines

- CXCL16
- RANTES MIP- α MIP- β
- IP-10
- CCL25

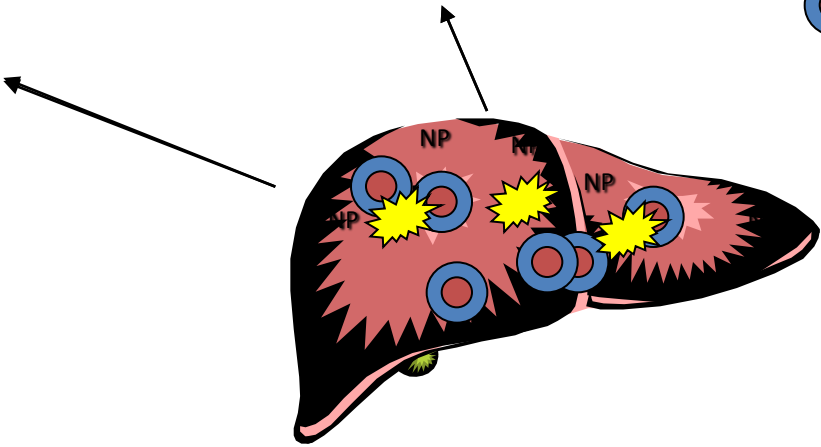


Peripheral lymphocytes



Chemokines receptors

- CCR6
- CCR5
- CXCR3



Liver inflammation
Stimulation des toll-like
Bystander hepatitis
Receptors

. Immune mediated hepatic diseases. Classification according to the target cell.

Target cell	Mechanism	Disease
Hepatocytes	Hepatotropic viruses infection →	Chronic viral hepatitis*
	Drugs →	Hepatitis / cholestasis
	Autoimmunity →	AIH*
	Alloimmunity →	Fetus Chronic rejection (liver transplant)
	“Apoptosis” →	Bystander hepatitis
Small interlobular bile ducts	Autoimmunity	PBC
	Alloimmunity	Acute rejection (liver transplantation) Graft vs Host
	Drugs	Cholestasis / VBDS#
Small and large bile ducts	Autoimmunity (inflammatory)	SC*

AIH: Autoimmune Hepatitis

PBC: Primary Biliary Cirrhosis

SC: Sclerosing Cholangitis

* These diseases can occur in immune competent and in immune deficient patients (acquired or inherited immuno deficiency)

Vanishing bile duct syndrome

.Clinical and laboratory data according to the main cellular target.

	Symptoms & signs	Laboratory data	Autoantibodies	Histology Predominant features
Hepatocytes*	Fatigue +	↑↑↑ ALT/AST ± GGT Hyper IgG Liver failure	SMA ANA LKM1 LC1 SLA	Interface hepatitis Portal tracts { Lymphocytes +++ Plasmocytes ++ (variable) Intralobular inflammation Bridging necrosis
Cholangiocytes / Bile ducts	Fatigue +++ Pruritus Jaundice	↑ ALT/AST ↑↑↑ GGT Hyper IgM Hyper IgG (≅30% of SC)	Anca AMA ANA	Periductular granulomas (PBC) Periductular fibrosis (SC) Portal tract fibrosis

* In AIH: Predominance ♀ / Incidence variable according to age

LKM with different specificity can be found in HBV HDV chronic co-infections.

. Clinical and laboratory data in particular causes of immune related liver injury.

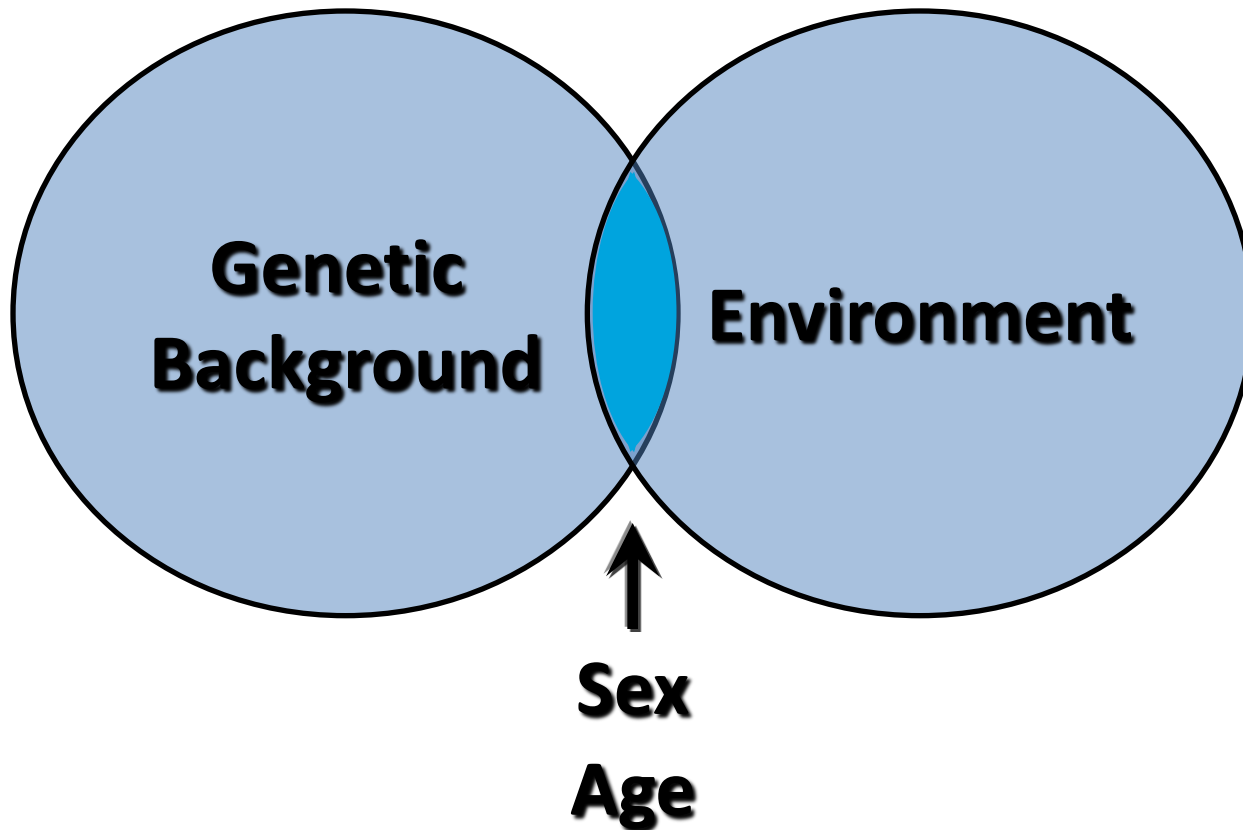
	Symptoms & signs	Laboratory data	Autoantibodies	Histology Predominant features
Innate Immune # system activation / cytokines storm	Related to the causing disease	↑↑ ALT/AST ↑ GGT	ANA SMA	Intralobular inflammation
Alloimmune fetal hepatitis	Hepatic failure	±↑ ALT/AST	—	Lobular desorganisation Rosettes +++ Iron stockage
GCH-AIH	Fatigue Jaundice	↑↑↑ ALT/AST Liver failure	—	Giant cell transformation of hepatocytes
Drug induced	Fatigue Jaundice Pruritus	↑-↑↑↑ ALT-AST ↑-↑↑↑ GGT	ANA SMA LKM•	Centrolobular necrosis (↑) Neutrophiles (↑) Eosinphiles

Bytander hepatitis

- LKM with specific CYP reactivities

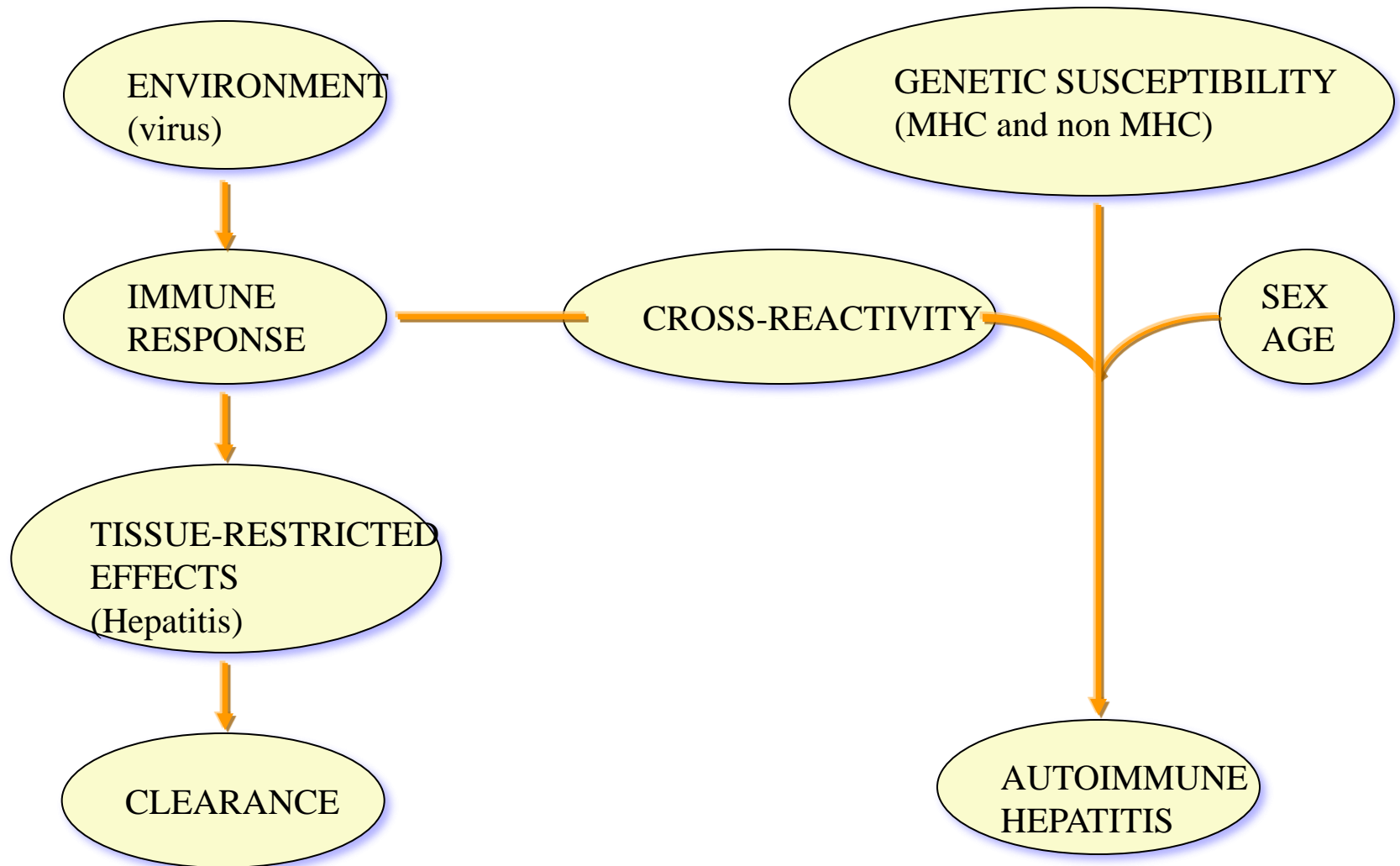
Autoimmune Liver Diseases

Pathogenesis

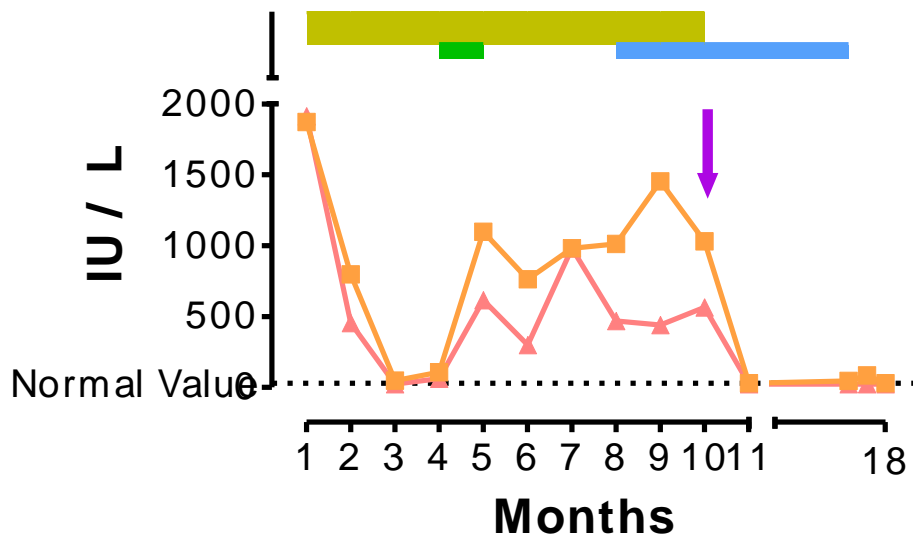
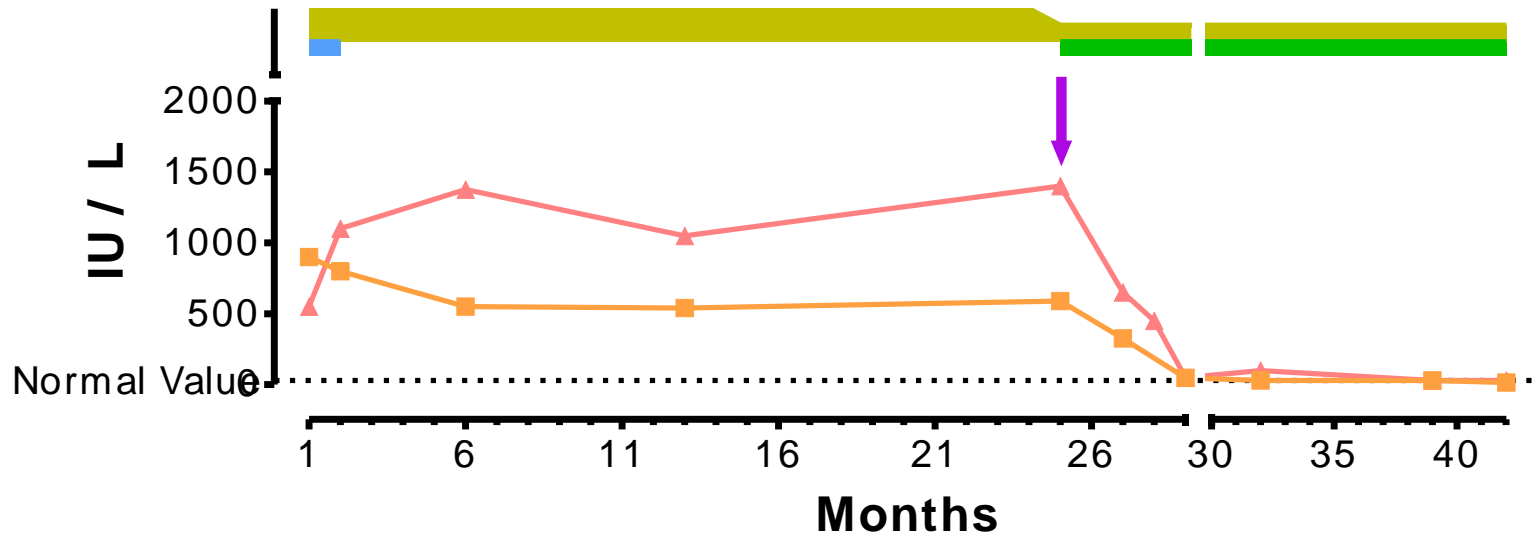


AUTOIMMUNE HEPATITIS

Pathogenesis



Treatment of Autoimmune Hepatitis (two children)



- ▲ AST
- ALT
- Prednisone
- MMF
- AZA
- ▼ Rituximab

Modifications of autoimmune diseases associated with pregnancy

- Multiple Sclerosis (MS), Rheumatoid Arthritis (RA)

- Pregnancy
 - Remission
- Post-partum
 - Relapse

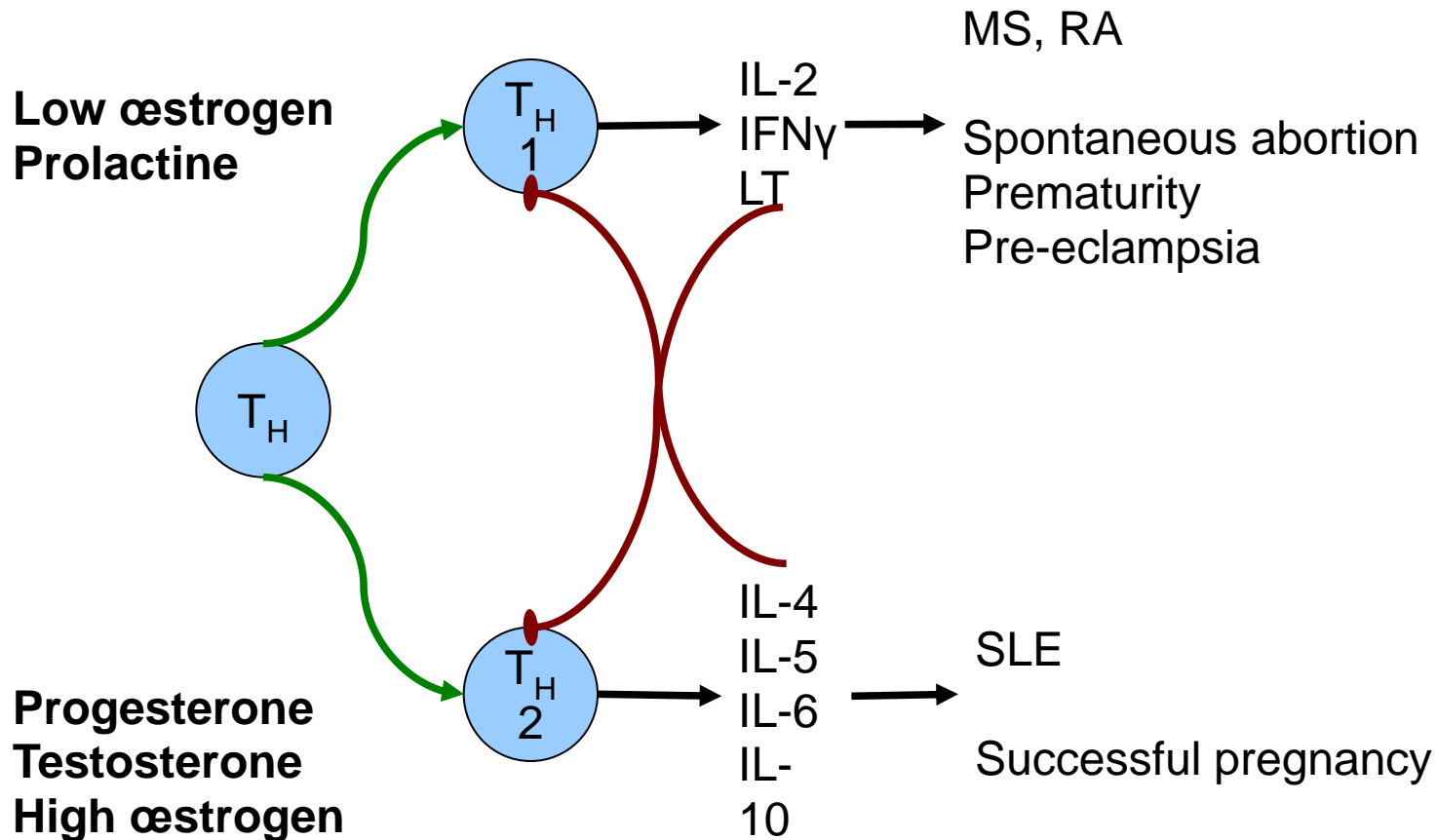


- Systemic Lupus Erythematosus (SLE)

Confavreux *et al.* 1998

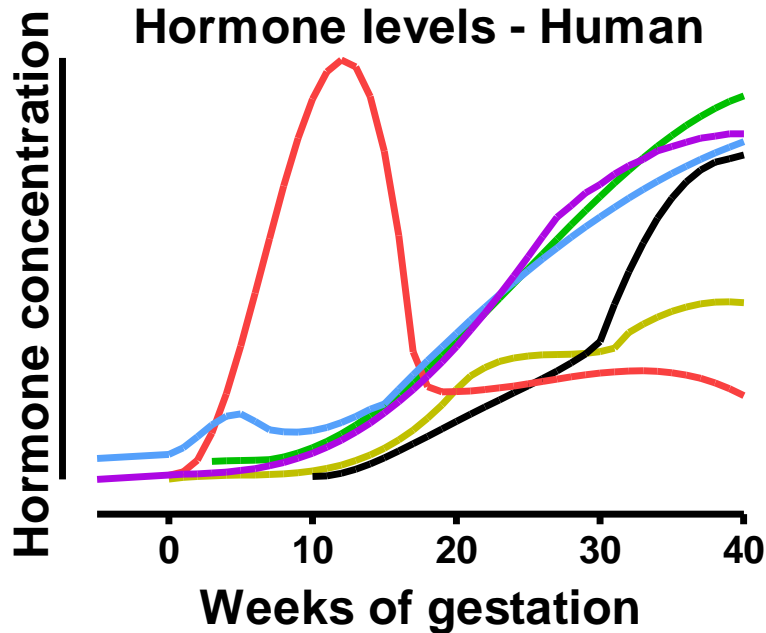
- Pregnancy
 - Flares and increased maternal mortality

Pregnancy modifies the balance of the immune response



Adapted from Challis 2009, Whitacre *et al.* 1999

Hormones during pregnancy



- Estrone
- Estradiol
- Estriol
- Human Chorionic Gonadotropin
- Progesterone
- Human Chorionic Somatomammotropin (Human Placental Lactogen)

- Estrone (E1)
 - Less abundant
 - Sole present post-menopause
- Estradiol (E2)
 - Predominant form, also present in males
 - High levels during ovulation and third trimester of pregnancy
 - Bind both ER α and ER β
- Estriol (E3)
 - Present only, and abundantly during pregnancy
 - Preferentially bind ER β

Estrogen receptors (ER) and the immune system

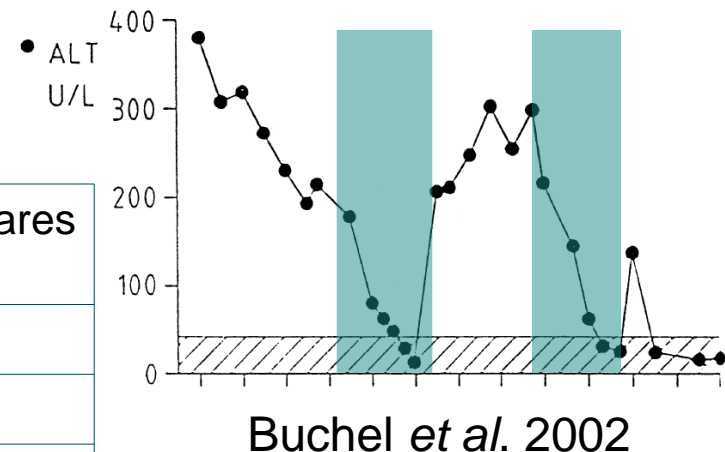
Cells	Origin	Specie	ER- α	ER- β
Neutrophiles	Peripheral blood	Humans	✓	✓
Monocytes	Peripheral blood	Humans	✓	✓
Macrophages	Peripheral blood	Humans	✓	✓
Macrophages	Peritoneal cavity	Mice	✓	✓
Eosinophiles	Peritoneal cavity	Rats	✓	
Mastocytes	HMC- 1	Humans	✓	
Mastocytes	Bone marrox	Mice	✓	
Mastocytes	HMC- 1	Humans		✓
Mastocytes	Bone marrow	Mice		✓
Dendritic	Bone marrow	Mice	✓	✓
NK	Spleen	Mice	✓	✓
B Lymphocytes	Spleen	Mice	✓	
T Lymphocytes	Peripheral blood	Humans	✓	
B Lymphocytes	Spleen	Mice		✓

Sexual differences?

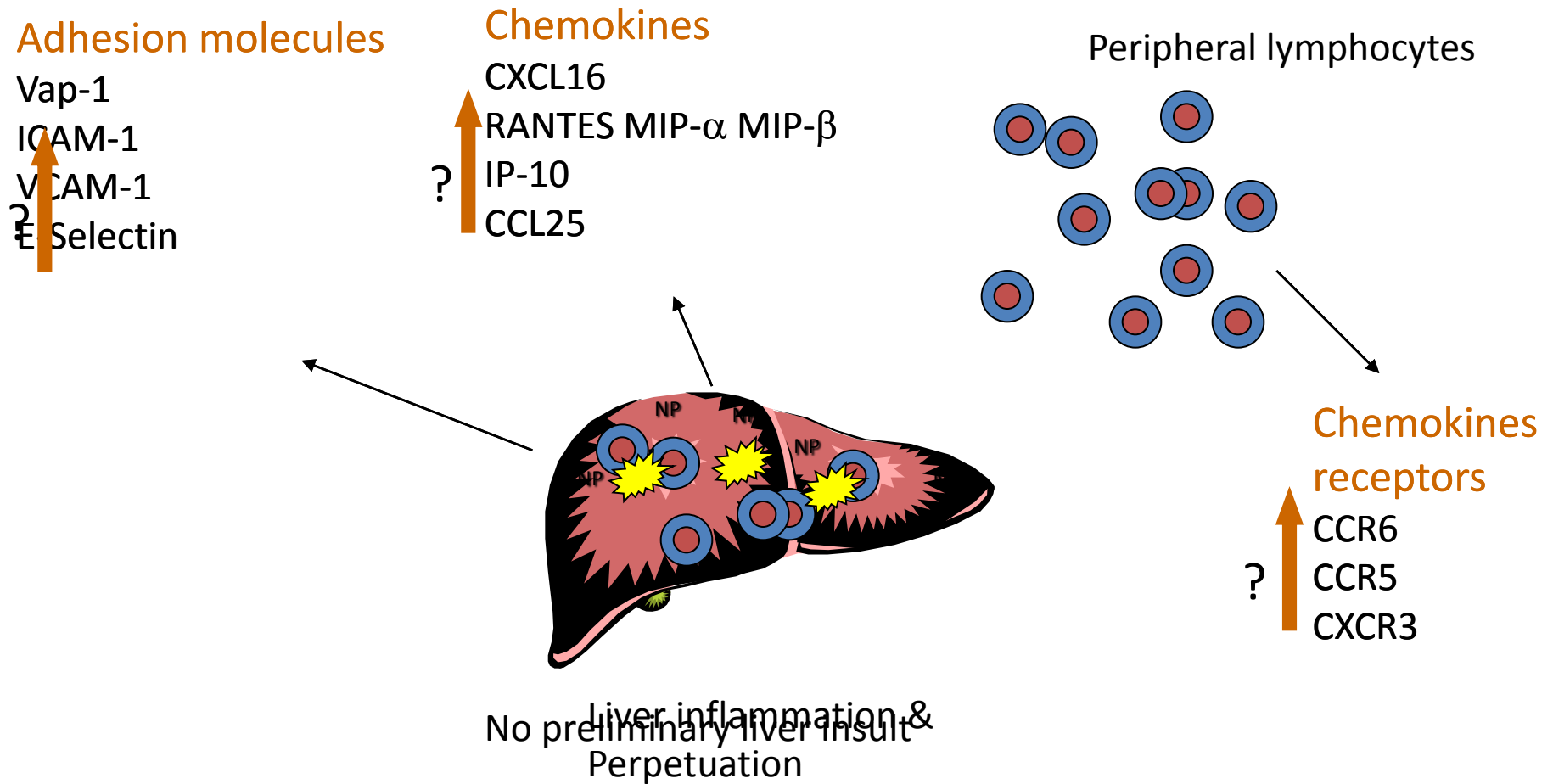
Autoimmune hepatitis with pregnancy

- 70% (type 1) - 90% (type 2) patients are women
- Modern therapies to treat autoimmune hepatitis
 - Restored fertility of patients
 - Increased long term survival
 - Increased the number of pregnancies
- Remissions during pregnancy
- Relapses or flares post-partum

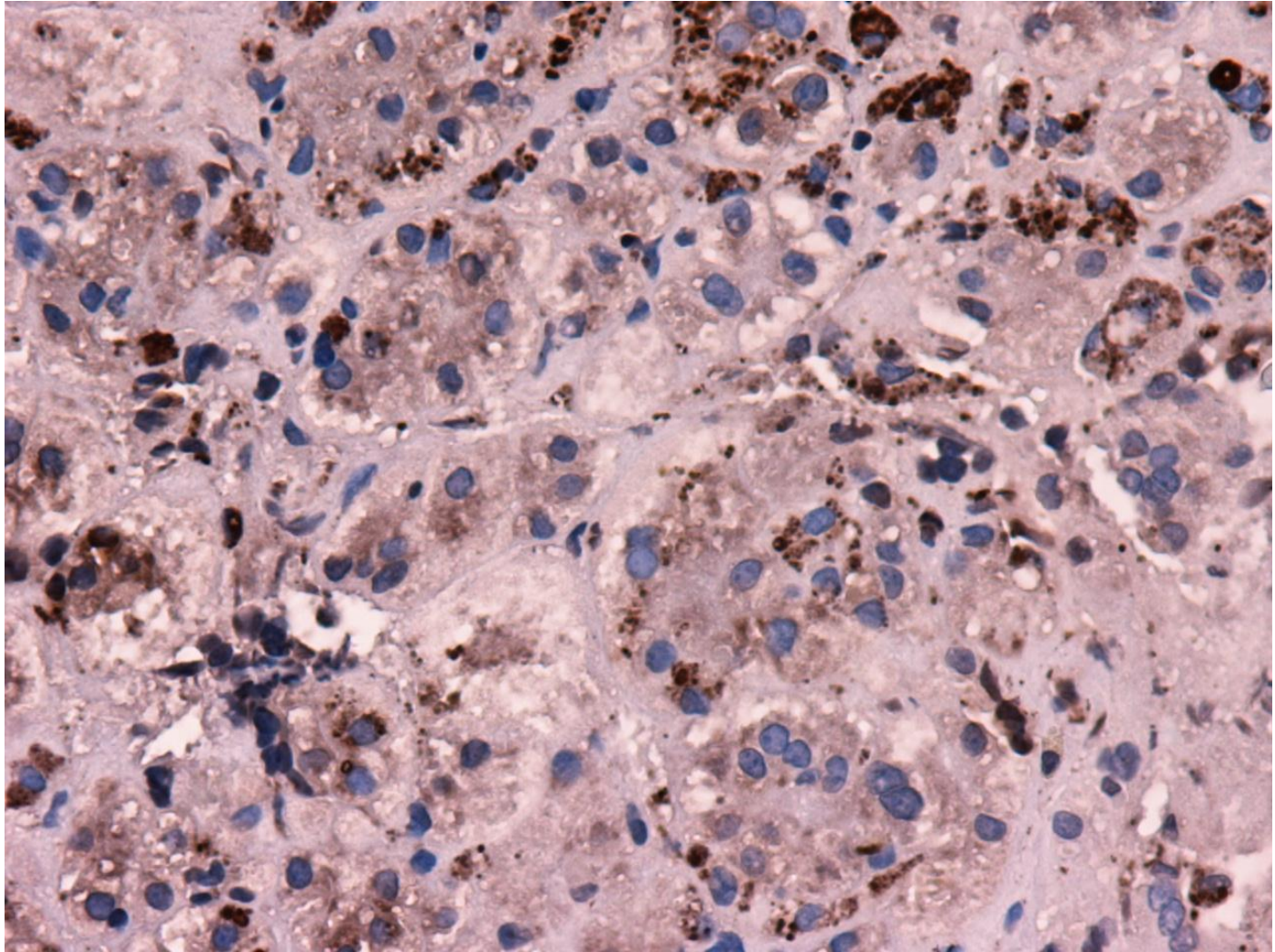
	Remission	Post-partum flares
Schramm <i>et al.</i> 2006	73%	52%
Werner <i>et al.</i> 2007	89%	29%
Raquel <i>et al.</i> 2009	63%	30%



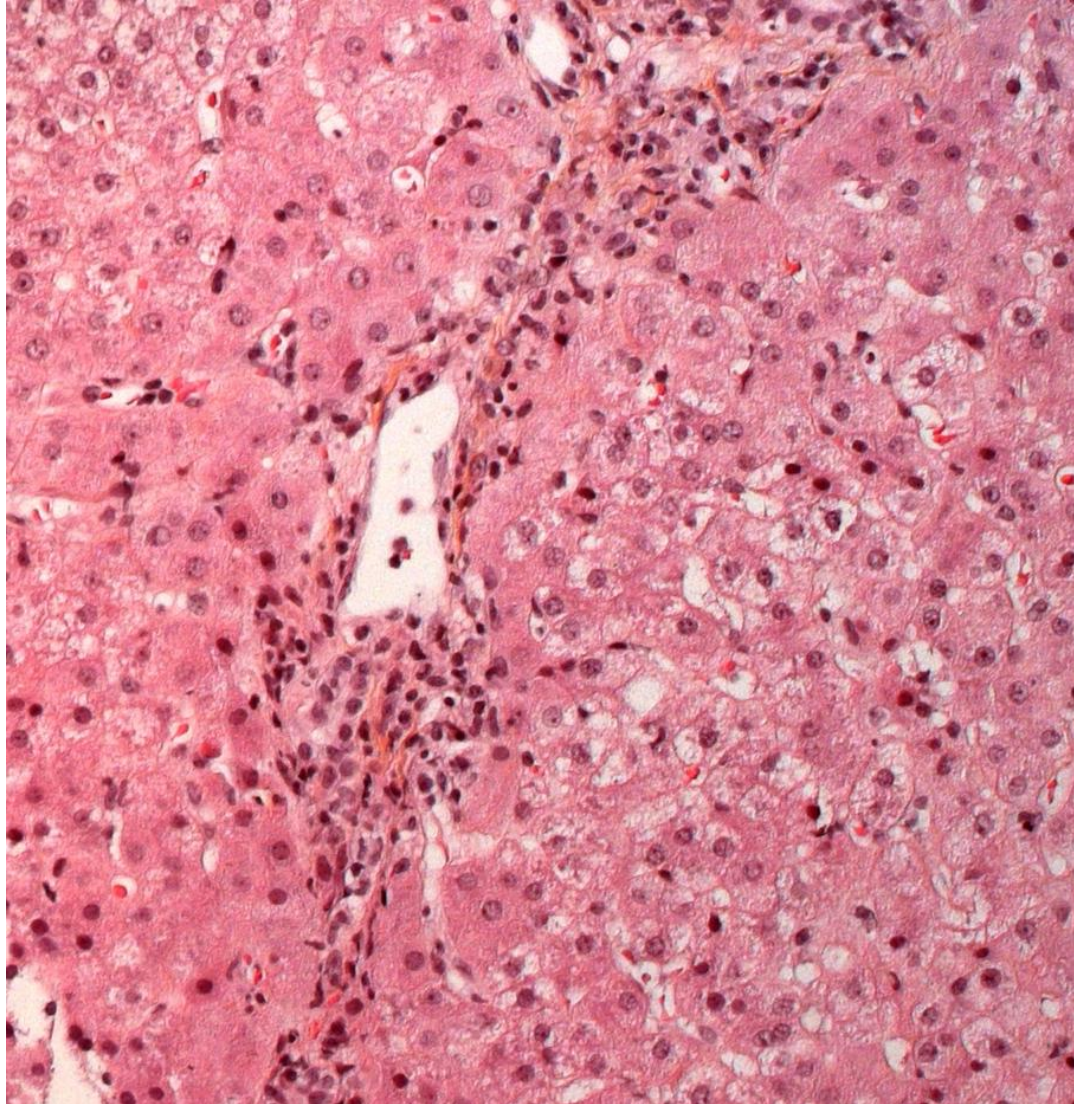
Mechanism of lymphocyte migration & inflammation

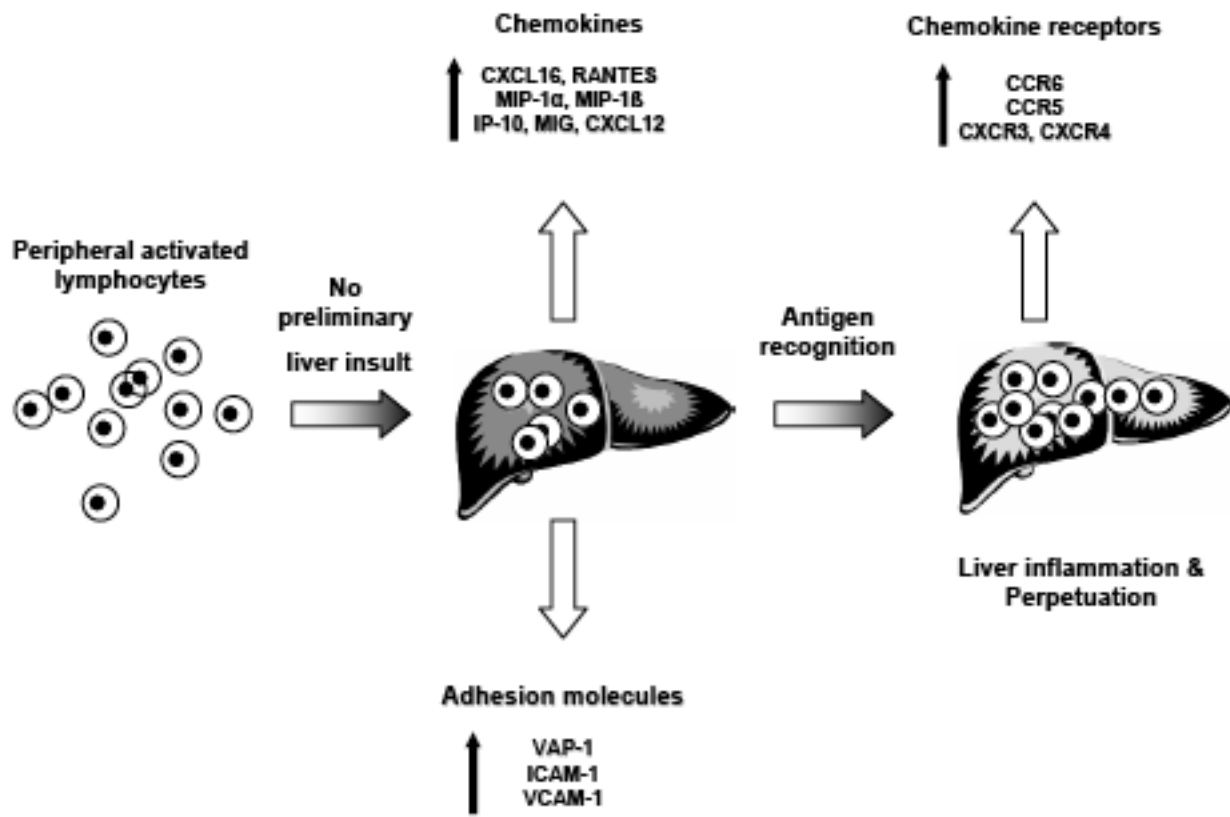


GCH-AIA



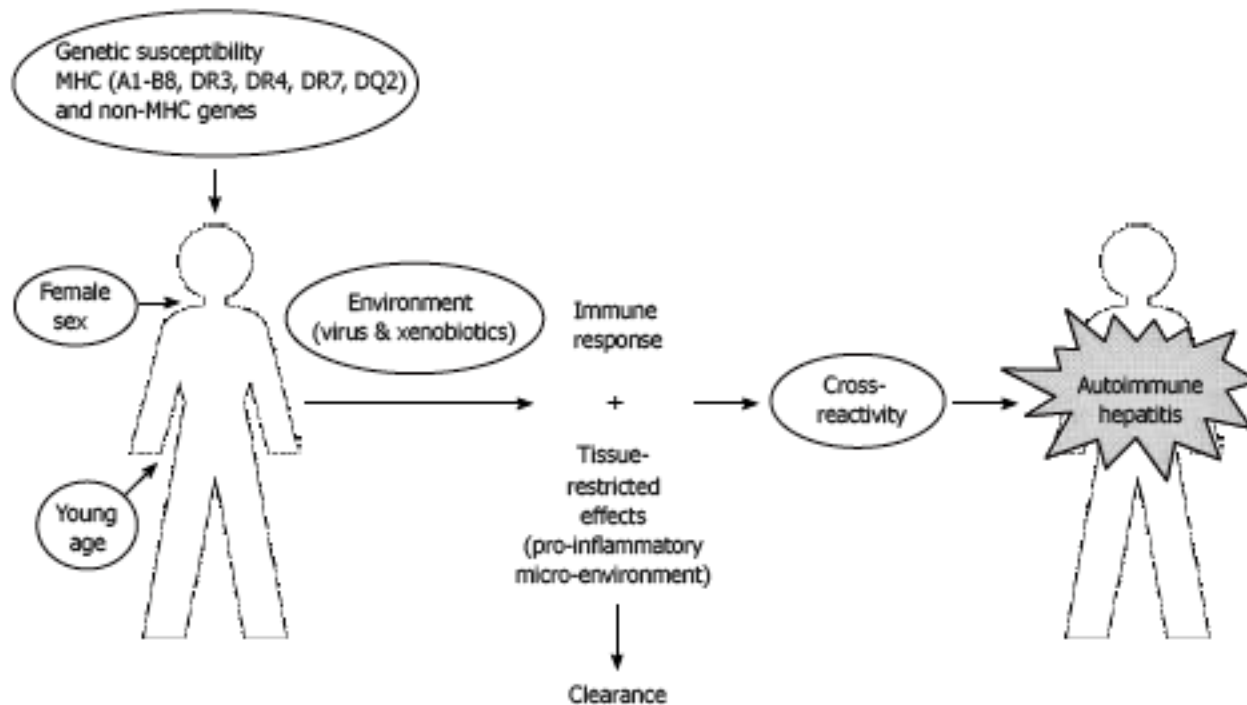
REJECTION-ENDOTHELIALITIS





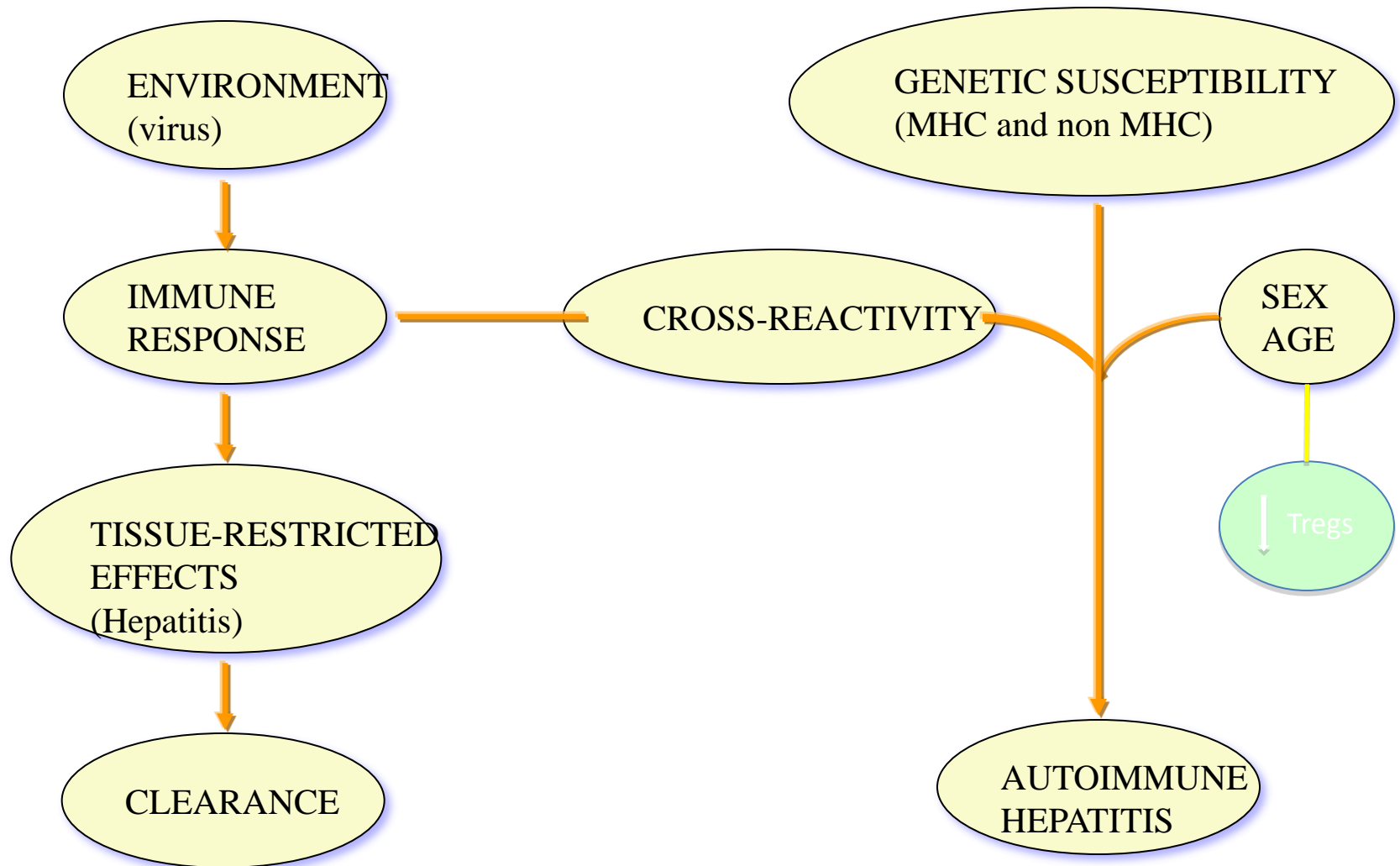
FOIE ET SYSTEME IMMUNITAIRE

PATHOGENESE DE L'HAI



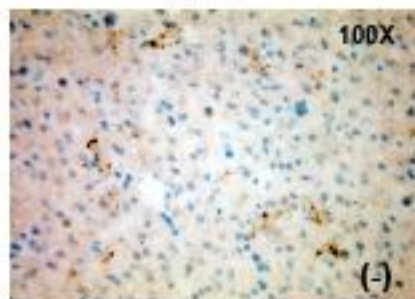
AUTOIMMUNE HEPATITIS

Pathogenesis

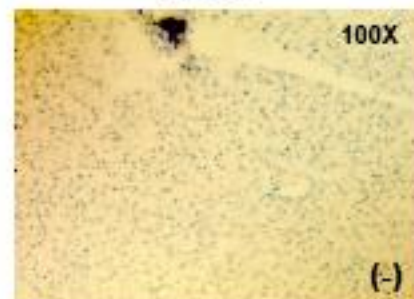


Control mouse

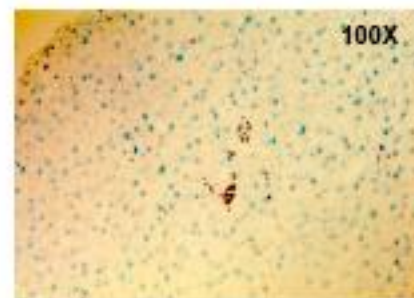
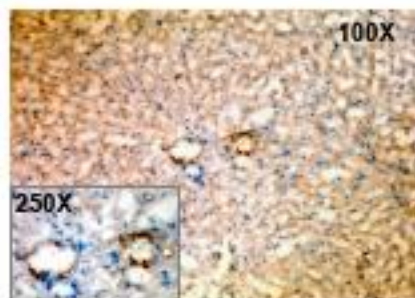
IP-10



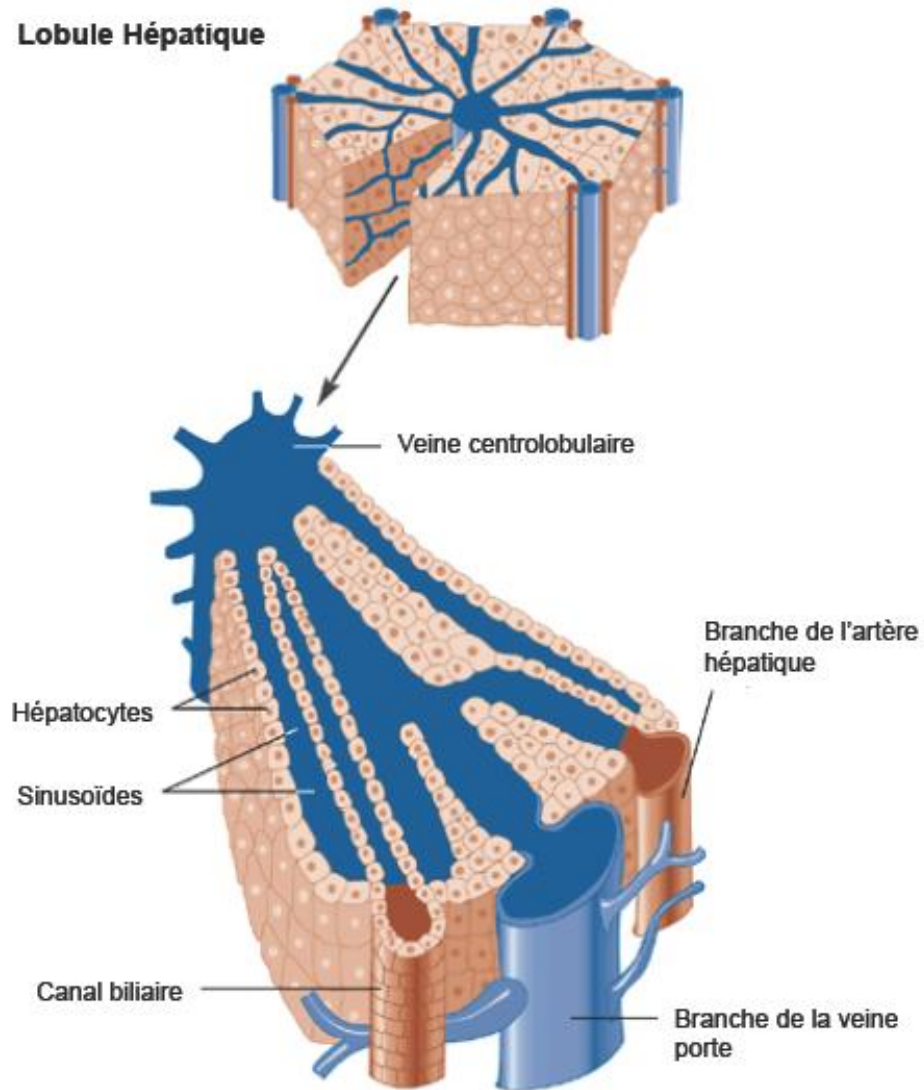
CXCR3



Murine model
of AIH

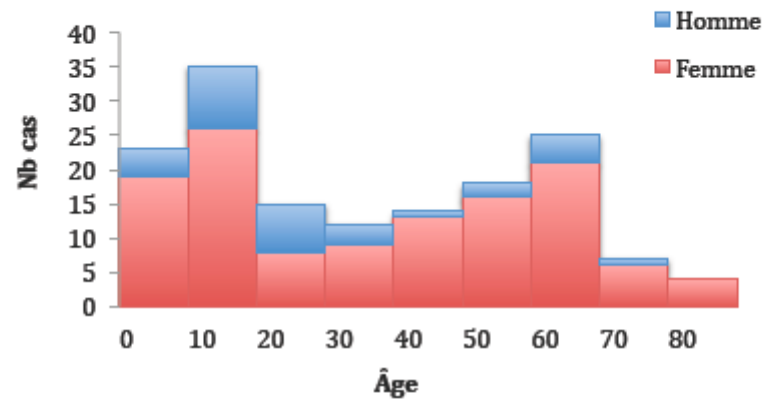


Hígado-y sistema inmunitario

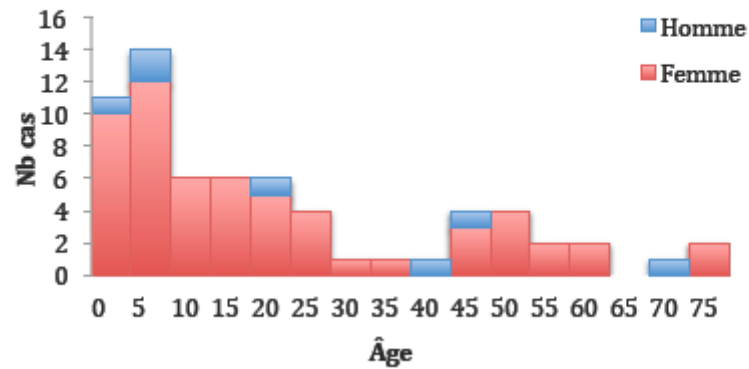


Hépatite autoimmune

Hépatite autoimmune de type 1

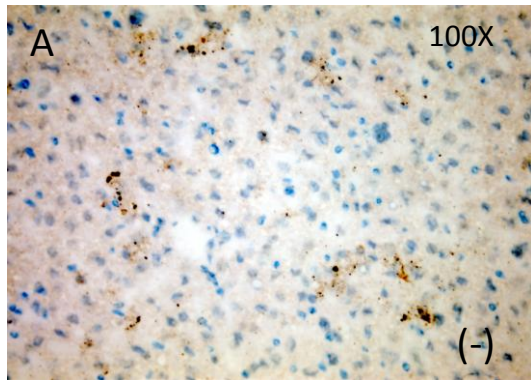


Hépatite autoimmune de type 2

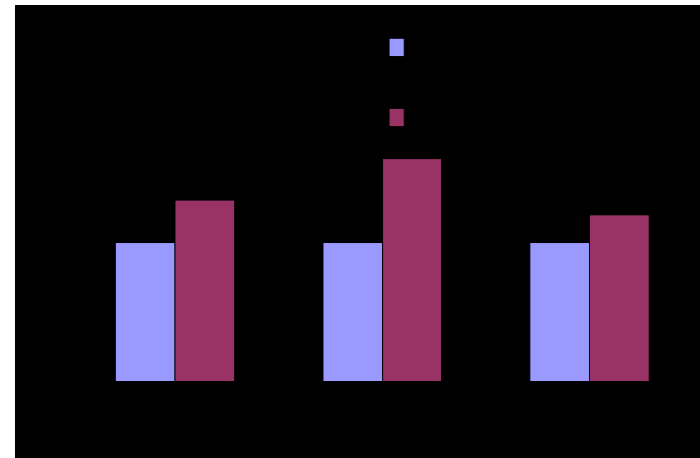
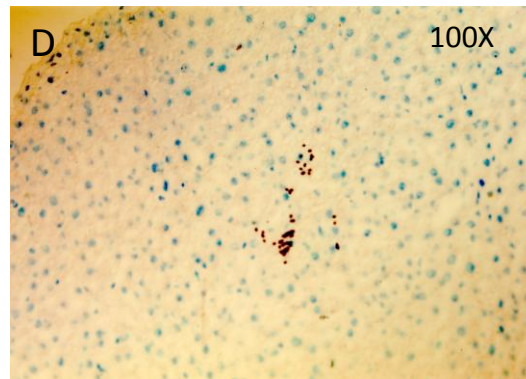
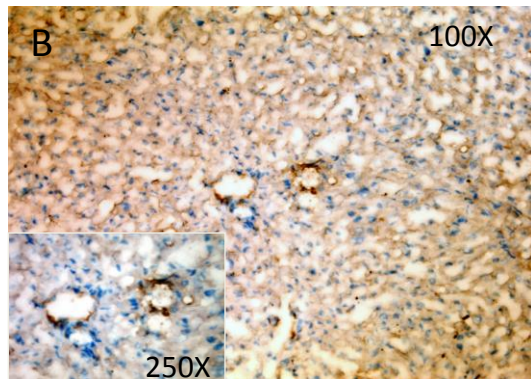
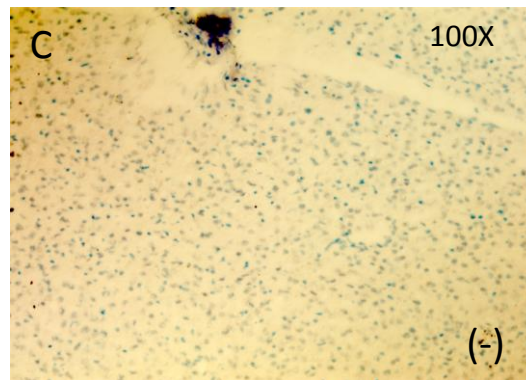


AIH and chemokines

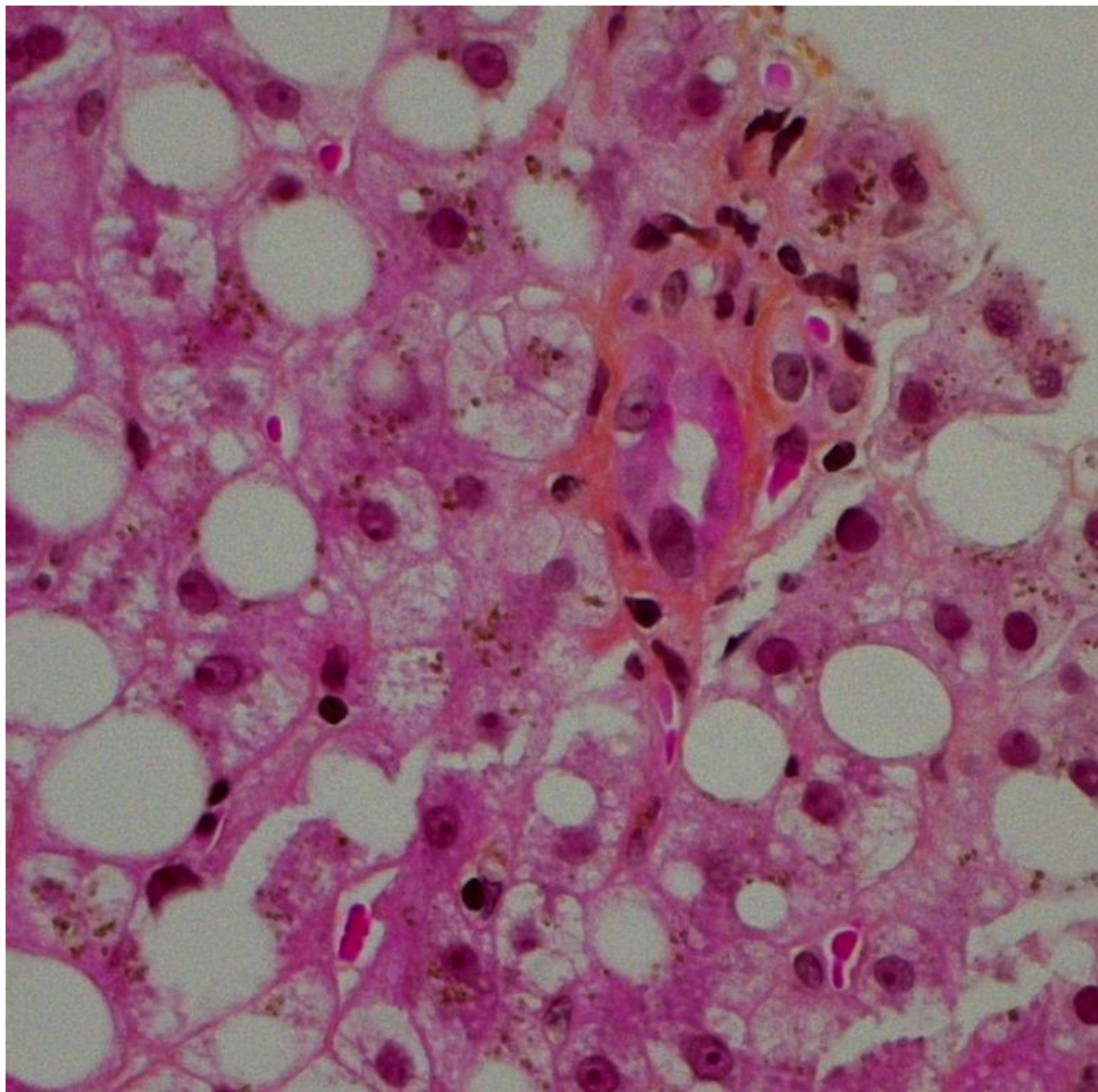
IP-10



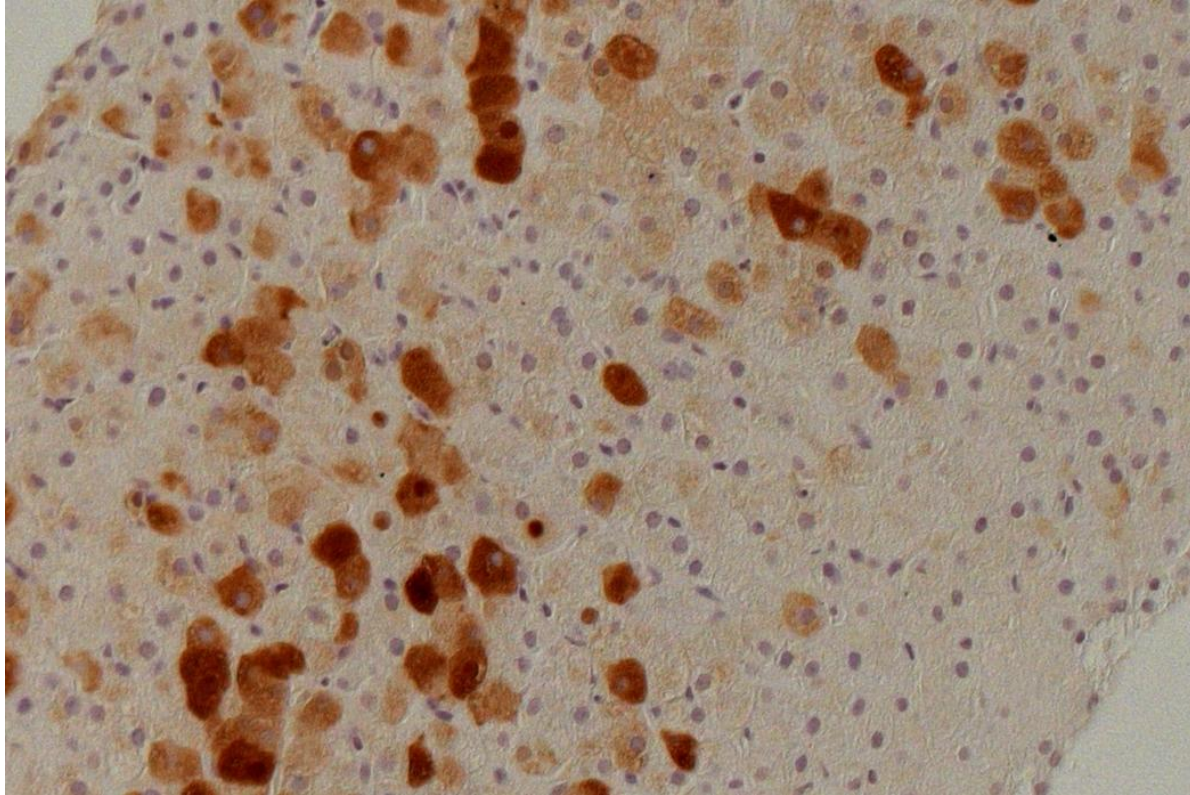
CXCR3



GVH



HBV-AgHBs



AUTOIMMUNE HEPATITIS IN CHILDREN

Clinical and laboratory criteria contributing to the diagnosis

- ✦ **Female gender**
- ✦ **AP/AST/set ratio < 1.5**
- ✦ **Serum globulins (IgG) above normal**
- ✦ **Autoantibodies (ANA, SMA, LKM1, LC1)**
- ✦ **Negative hepatitis viral markers**
- ✦ **Negative drug history**
- ✦ **Other autoimmune disorders**
- ✦ **Histological features**
- ✦ **Complete response to immuno-suppressive therapy**



GCH_AIA

