Hepatitis virus immunity

Mar 9, 2005

Rehermann and Nascimbeni review

Crispe review

HBV & HCV infection outcomes

- Both viruses cause immune-mediated active and chronic hepatitis
- HBV
  - Vertical transmission = chronic hepatitis
  - Adult infection = protective immunity
- HCV
  - Adult infection = 60-80% chronic hepatitis

Clinical features

Feature	Hepatitis B	Hepatitis C
Worldwide	350 million infected	170 million infected
United States	1 million infected	4 million infected
Vertical transmission	Mother to neonate Chronic hepatitis	Rare -
Horizontal transmission	IV drug use, parenteral, sexual Recovery	IV drug use, parenteral, sexual Chronic hepatitis
Vaccine	Yes	No

Molecular virology

Feature	HBV	HCV
Structure	42 nm enveloped partially dsDNA	50 nm enveloped +stranded RNA
Family	Hepadnaviridae	Flaviviridae
Receptor	Unknown	Includes CD81
Mutation rate	Low (10^{-5}/base)	High (10^{-3}/base)
Genotypes	8; low divergence	6 with >50 subtypes

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Source: Figure 1 in Rehermann, B., and M. Nascimbeni. "Immunology of hepatitis B virus and hepatitis C virus infection." *Nature Review Immunology* 5, no. 3 (2005).

HBV molecular virology

- Relaxed circular 3.2-kb genome
  - Full-length negative strand, 5´ viral RT
  - Partial positive strand, 5´ oligoribonucleotide
- cccDNA template for transcription of 4 viral RNAs in nucleus
  - Exported to cytoplasm and translated
  - Longest RNA also serves as template for HBV replication in nucleocapsids in the cytoplasm
  - Some DNA and nucleocapsids return to nucleus
  - Others bud into ER & are secreted via golgi

HCV molecular virology

- ssRNA (+) 10K nucleotides
- Single long ORF flanked by 2 UTRs
- Replicates in the cytoplasm
  - Translation initiated by internal ribosomal entry site in 5´ UTR
- Polyprotein processed into structural and non-structural proteins
  - Combine with viral RNA to form membrane-associated replication complexes
  - Nucleocapsids bud into cytoplasmic vesicles

Acute HBV infection in adults

- HBV DNA is detectable in circulation within 1 month of infection
  - Remains at a low level (10^2-10^4 genome equivalents/ml) for up to 6 weeks
  - HBeAg and HBsAg reach peak levels
  - HBcAg-specific IgM appears early and IgG persists for life, regardless of outcome
- T cell-mediated liver damage begins to be apparent 10-15 weeks after infection
  - Most viral DNA is cleared by this time

Acute HBV infection in adults

- >90% of acutely infected adults resolve all clinical signs, develop HBeAg- and HBsAg-specific antibodies, clear HBeAg and HBsAg from circulation, and maintain lifelong protective immunity
- Despite complete clinical recovery, trace amounts of HBV DNA persist and are controlled by humoral and cellular immune responses

Acute HCV infection in adults

- HCV reaches high levels in serum within 1 week after infection
  - Cellular immune response takes 1 month and humoral immune response 2 months
  - Clinical signs associated with T cell-mediated liver damage are rare
- Liver enzymes indicating tissue damage are detectable 8-12 weeks after infection
  - Viral RNA declines
  - Development of HCV-specific Ig is variable

Acute HCV infection in adults

- HCV-specific antibodies do not indicate the outcome of infection
- Most individuals develop chronic hepatitis with relatively stable viral titers (2-3 logs below that in the acute phase)
- Only a small proportion of patients recover and test negative for viral RNA
- Whether complete eradication occurs is controversial

Protective immunity to HBV

- Clinical recovery is associated with lifelong protective immunity
  - Trace amounts of virus persist
  - Reactivation with immunosuppression
  - Transmission via organ transplantation
  - Trace virus may maintain immune response
- Controversy regarding need to boost to maintain vaccine-induced HBsAg-specific immunity

Protective immunity to HCV

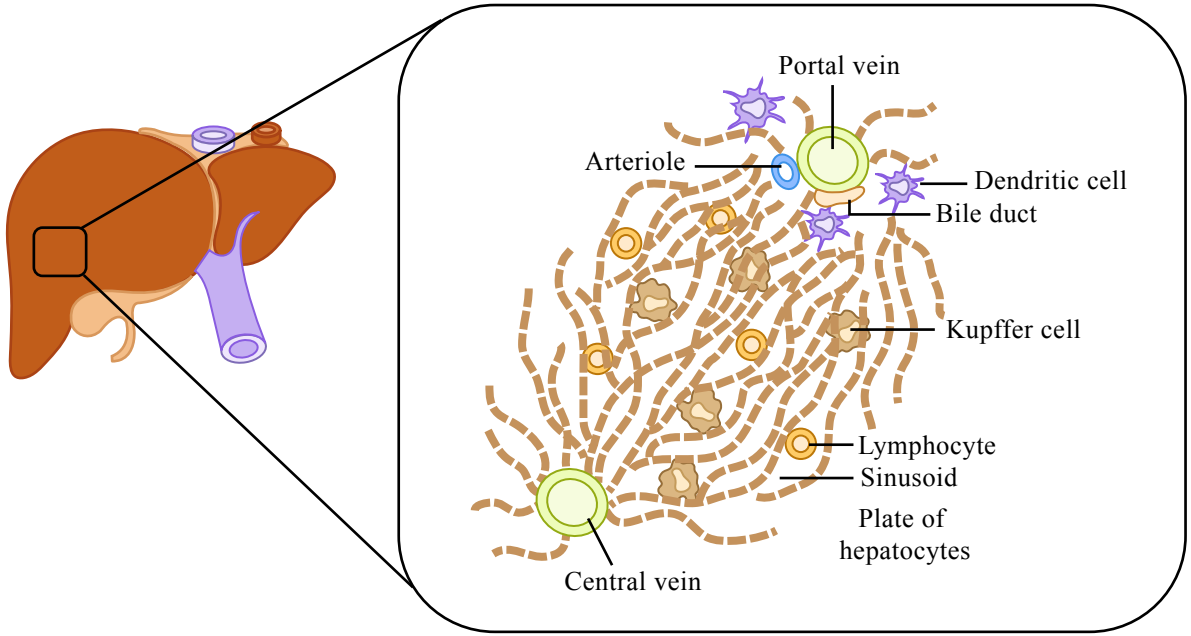
- Recovery is associated with HCV-specific T cells
  - B cell responses are variable, and may not persist
- Whether HCV is completely eradiated or trace amounts remain is controversial
- Protective immunity is not believed to be completely protective or lifelong
  - But data in humans are limited

Liver tolerance

- Portal blood is rich in bacterial products and food-derived antigens
- Malaria, HBV, and HCV all persist
- Allogeneic liver grafts can be established and maintained without immunosuppression
- Local presentation of Ag causes T cell inactivation, tolerance, and apoptosis

Immune cells in the liver

- Resident macrophages = Kupffer cells
  - Can sometimes be effective APCs
  - Also seem to be involved in tolerance
- Intrahepatic lymphocytes
  - CD8+ > CD4+
  - NK and NKT populations are enriched



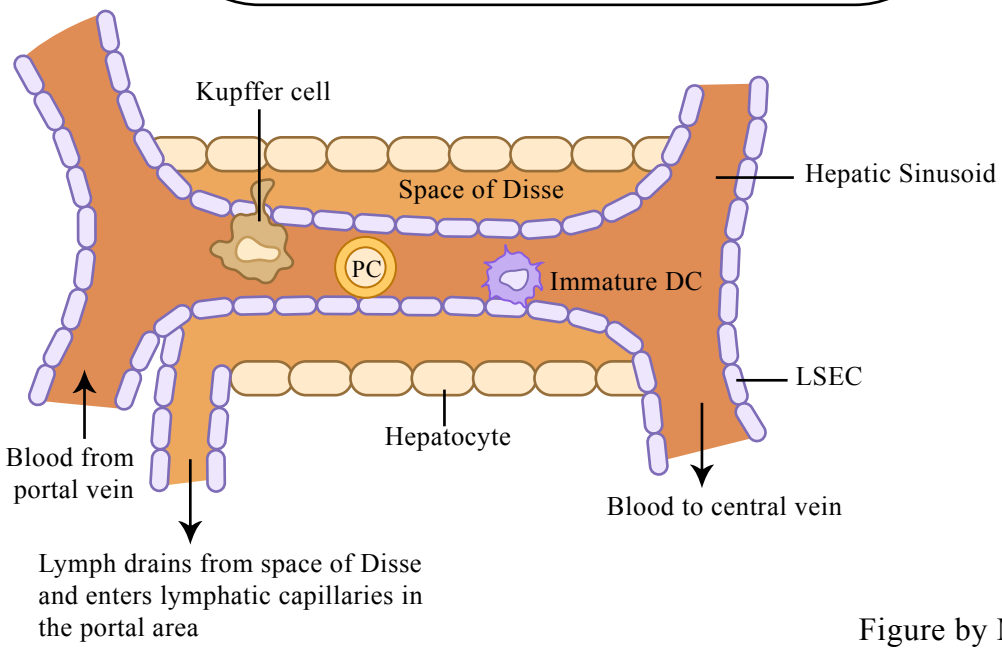
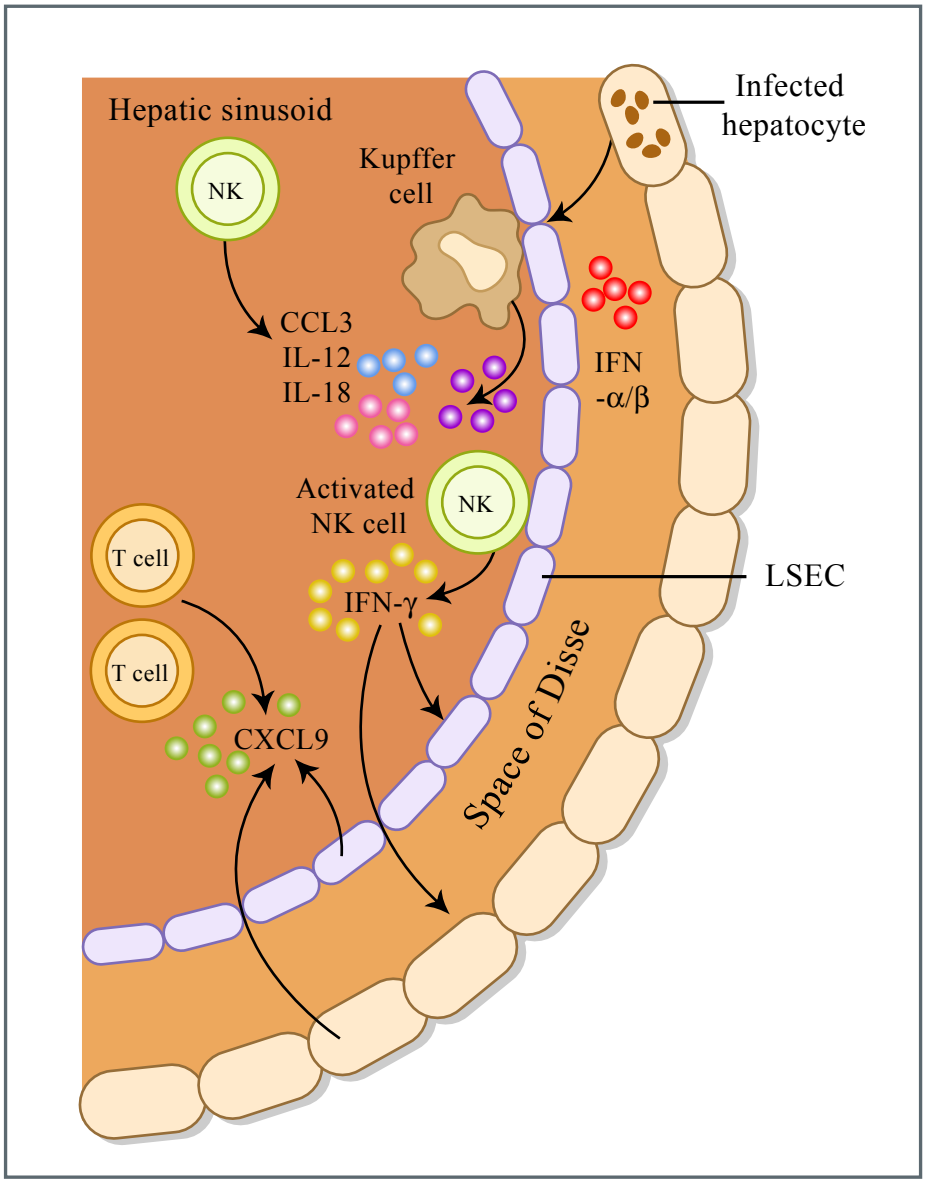


Figure by MIT OCW.

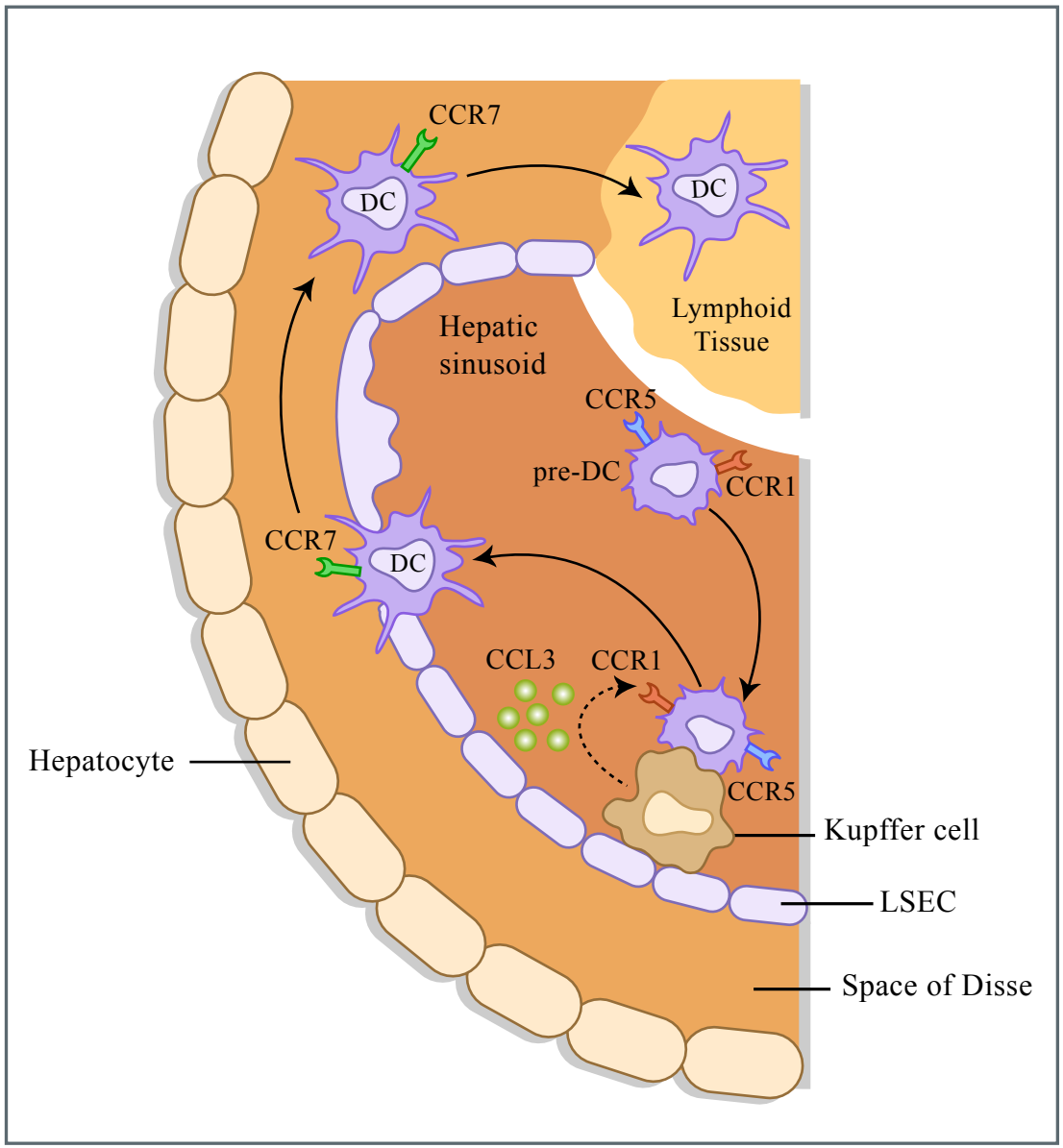
NK cells in the liver



- Important role in T cell recruitment
- In response to type 1 IFN, Kupffer cells produce CCL3 (MIP-1)
- Once activated by Kupffer cell IL-12, produce IFN-γ
- Induces other cells to secrete CXCL9 (MIG)

Figure by MIT OCW.

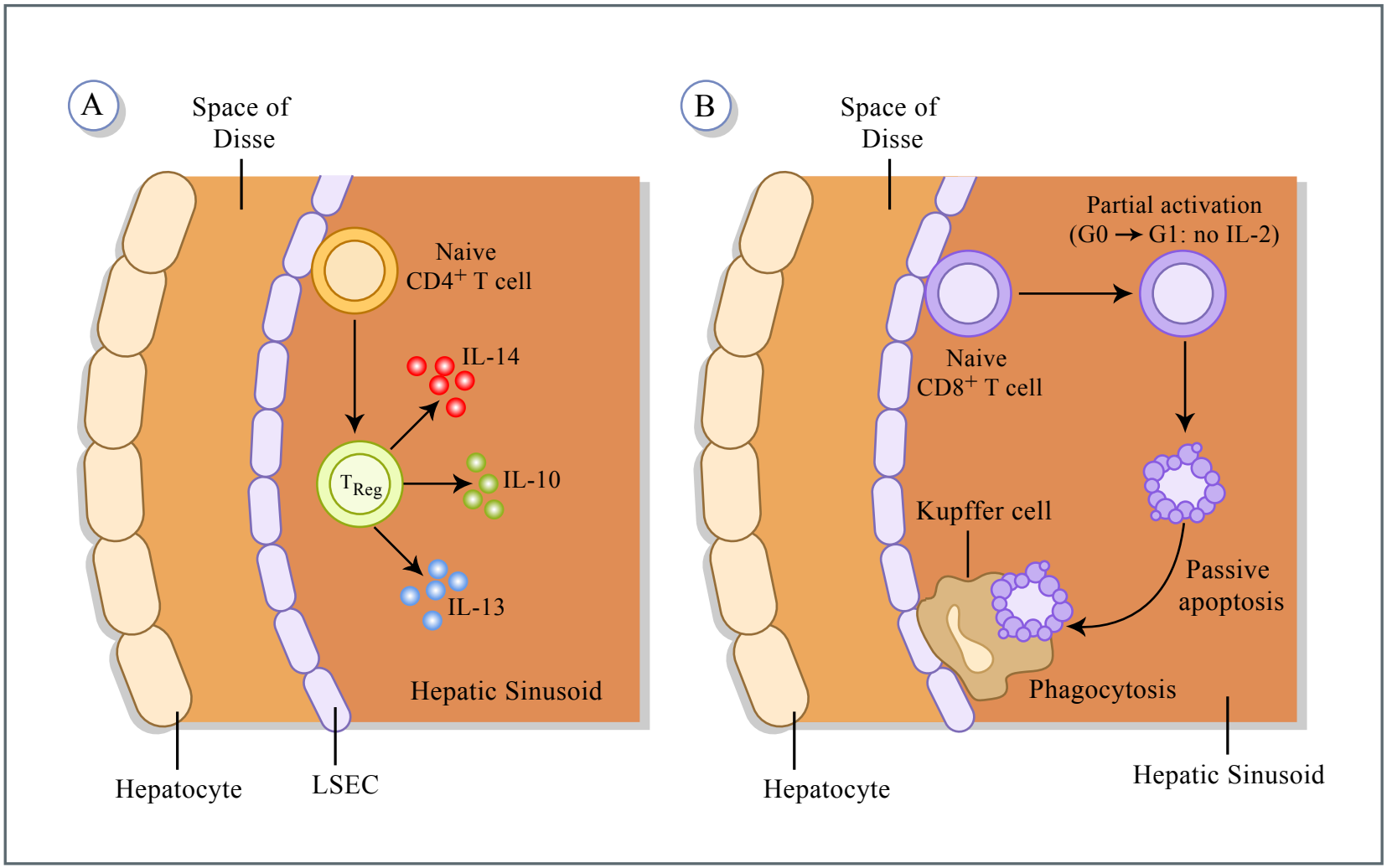
DC trafficking in the liver



- Also in response to Kupffer cell CCL3, immature DC respond via CCR1
- Downregulate CCR1 and CCR5, upregulate CCR7 and become responsive to CCL21
- Migrate to lymphoid aggregates in portal tracts and to LN

Figure by MIT OCW.

T cell tolerance in the liver



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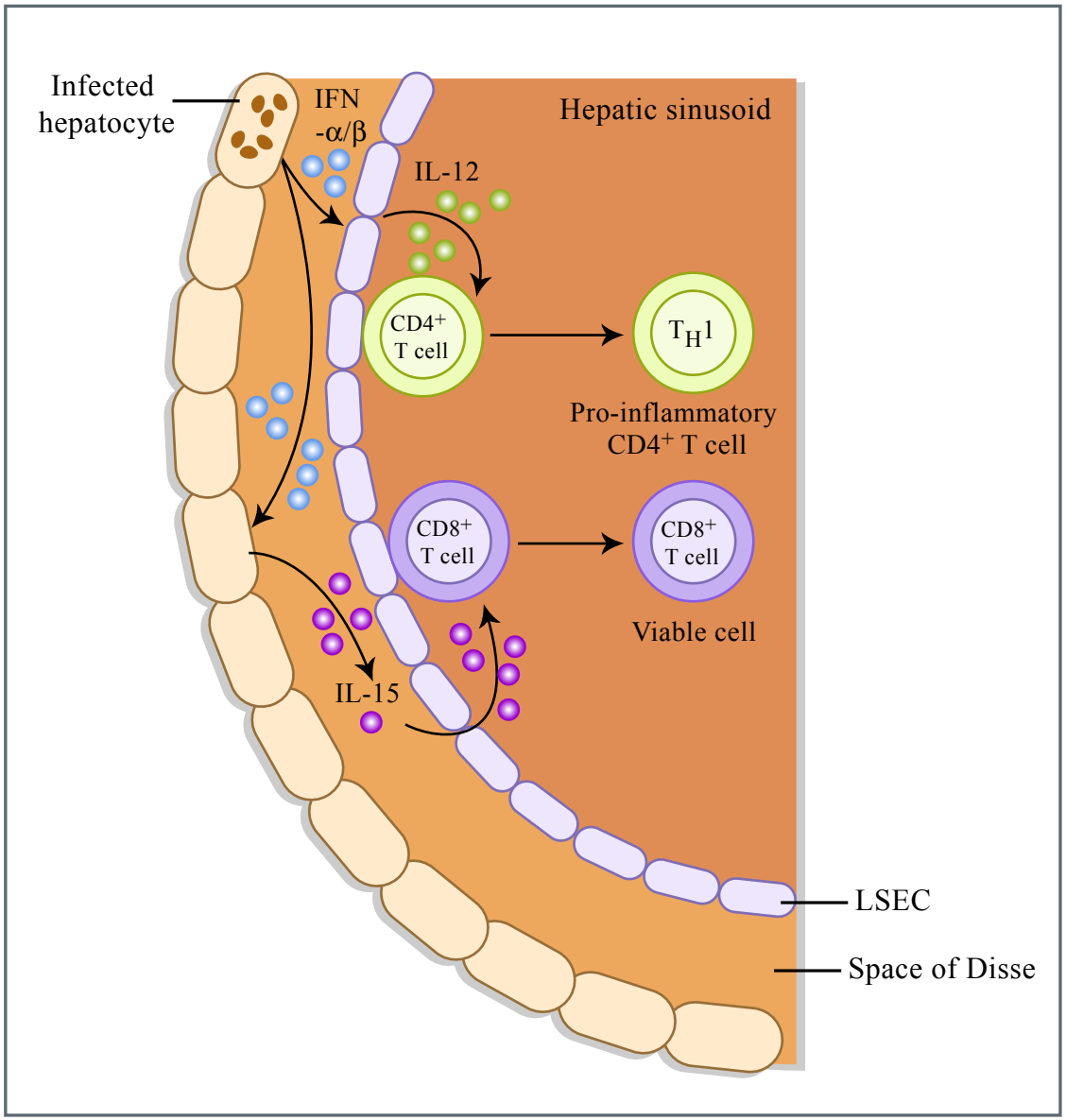
Overcoming base-line tolerance



- Hypothesis that type 1 IFN allows liver sinusoidal endothelial cells to produce IL-12
- Promotes differentiation of Th1 cells
- IL-15 serves as a survival factor for CD8+ T cells

Figure by MIT OCW.