



Cell-type specific expression analysis of liver transcriptomics with clinical parameters to decipher the cause of intrahepatic inflammation in chronic hepatitis B

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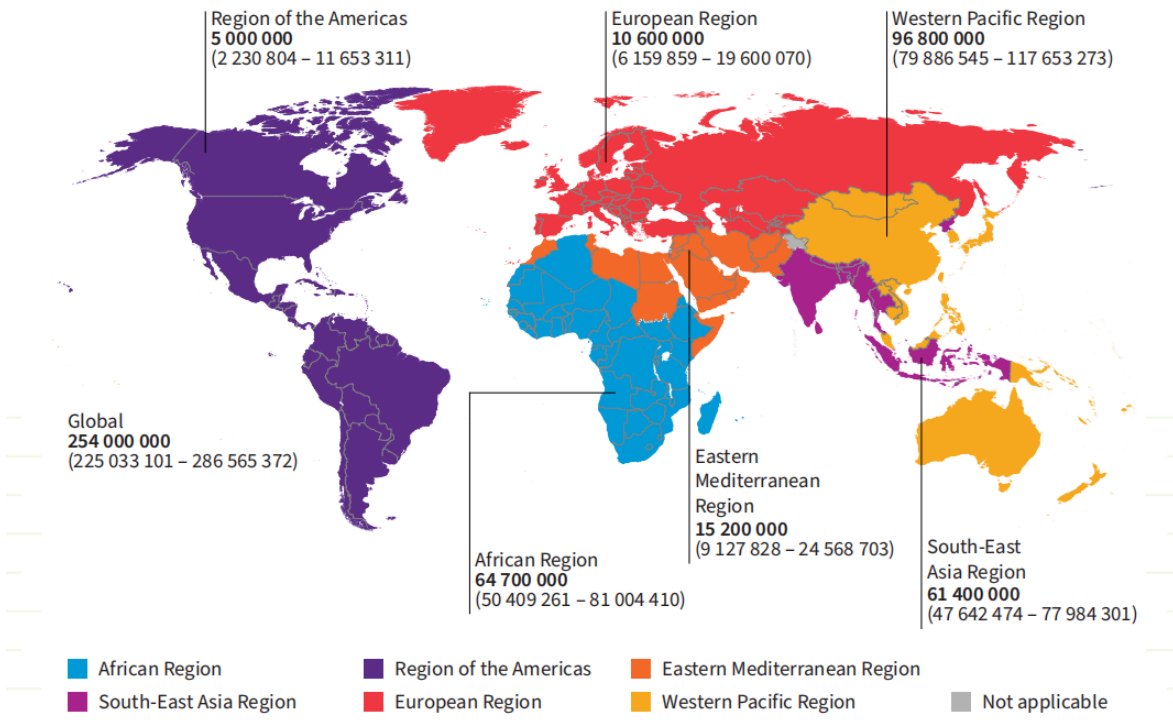


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2024. Cell-type specific expression analysis of liver transcriptomics with clinical parameters to decipher the cause of
intrahepatic inflammation in chronic hepatitis B. *iMeta* 3: e221. <https://doi.org/10.1002/imt2.221>



Introduction

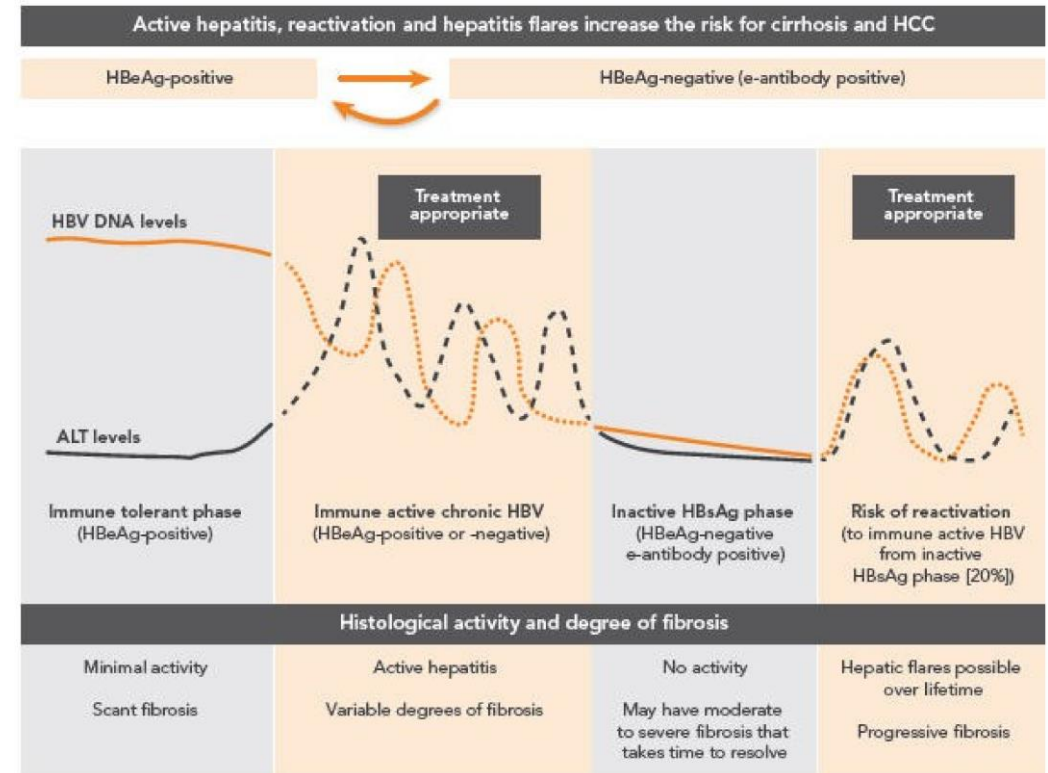
Prevalent cases of chronic hepatitis B (CHB) by WHO region, 2022



<https://www.who.int/publications/i/item/9789240091672>

Hepatitis B remains a major threat to human health.

Natural history of chronic HBV (CHB) infection



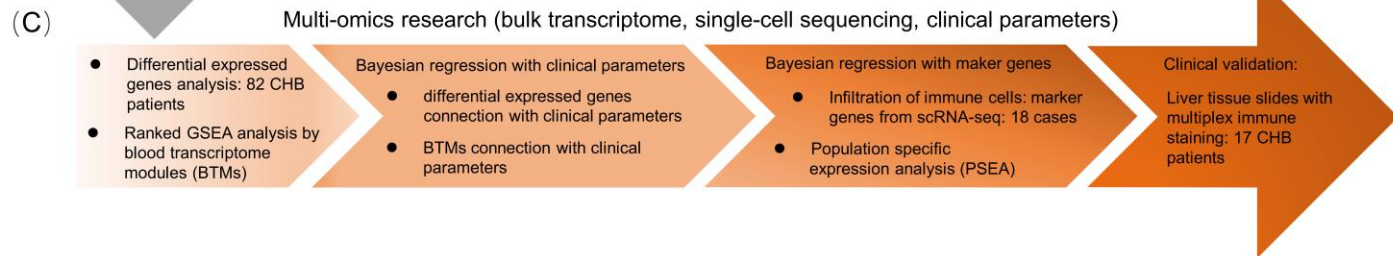
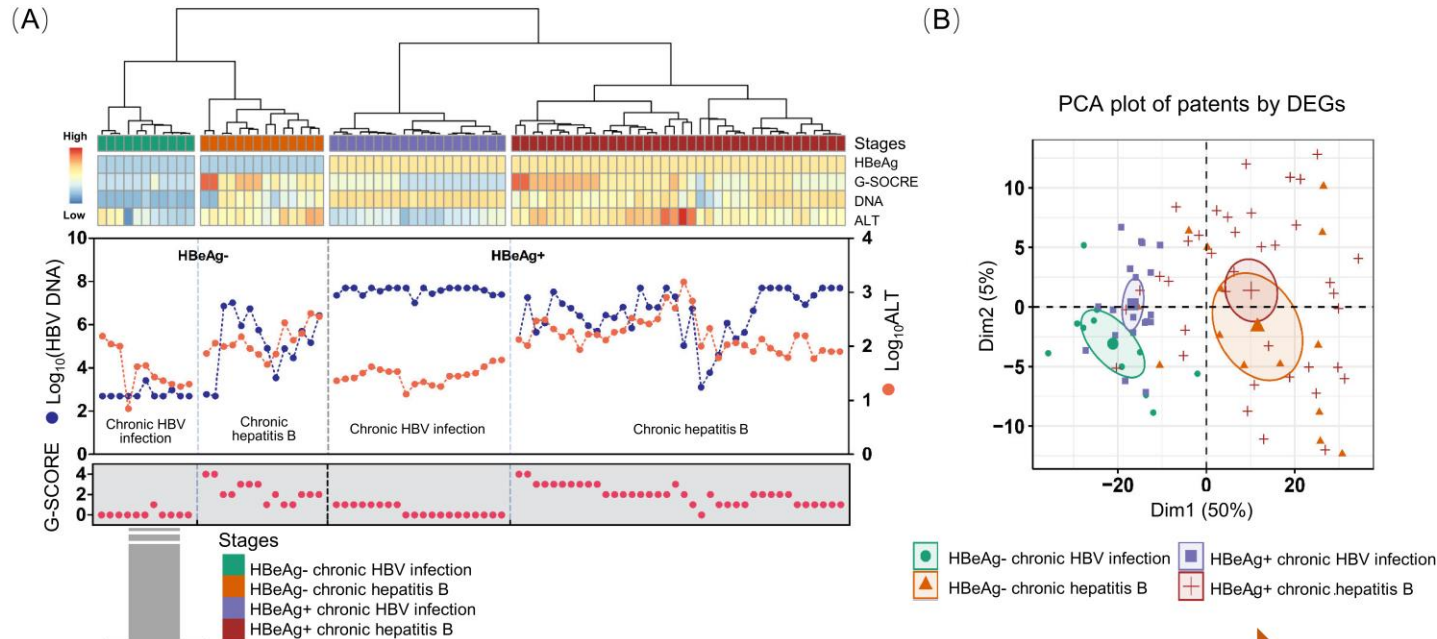
<https://www.who.int/publications/i/item/9789240091672>

- The natural history of chronic HBV infection is complex.
- In persistent HBV infection, host immune responses fail to control the virus, and progressive liver damage, cirrhosis, and cancer may occur.
- However, the mechanism of hepatic inflammation formation in CHB is not yet fully understood.

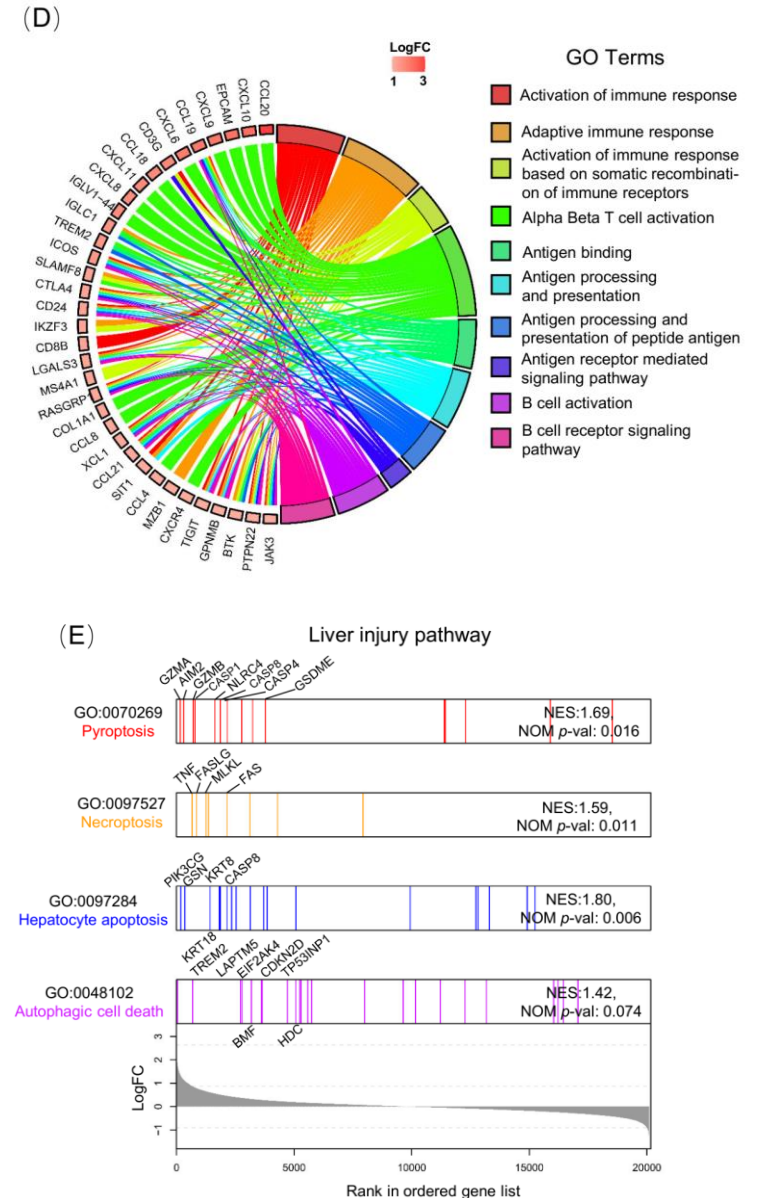
Results 1

Figure 1

- Clustering of CHB patients in four clinical phases
- Upregulated intrahepatic genes in chronic hepatitis



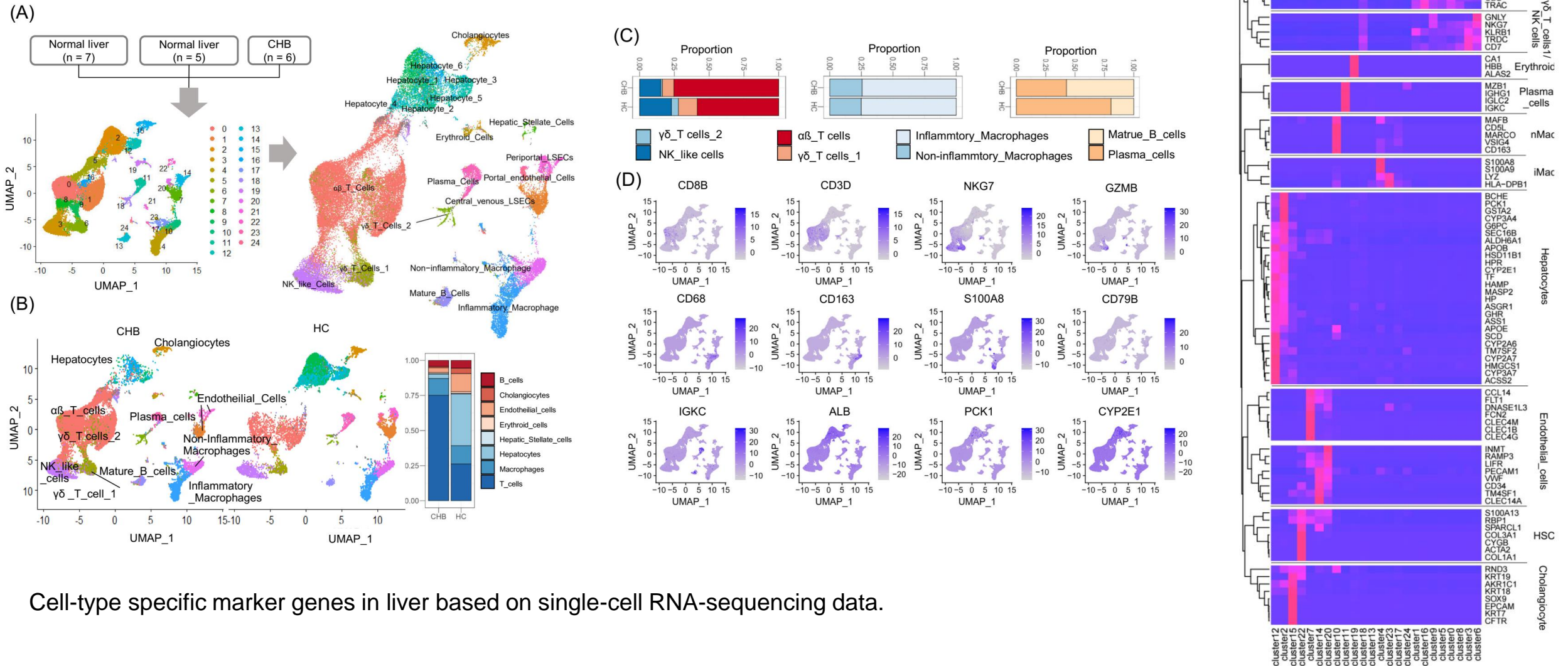
The findings confirm the association between host immune responses and liver injury in chronic hepatitis phases.



Results 2

Figure 2

Defining marker genes for each intrahepatic cell types

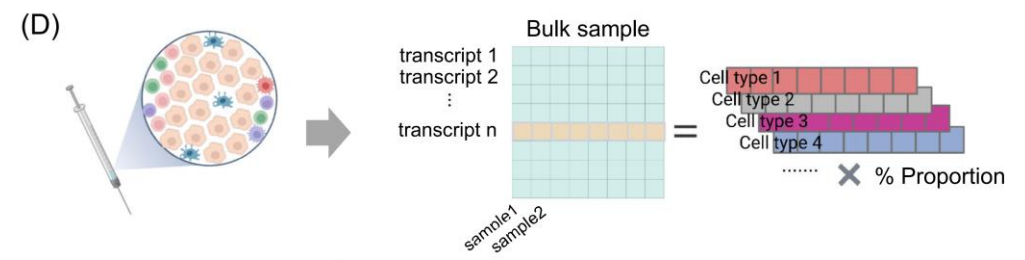
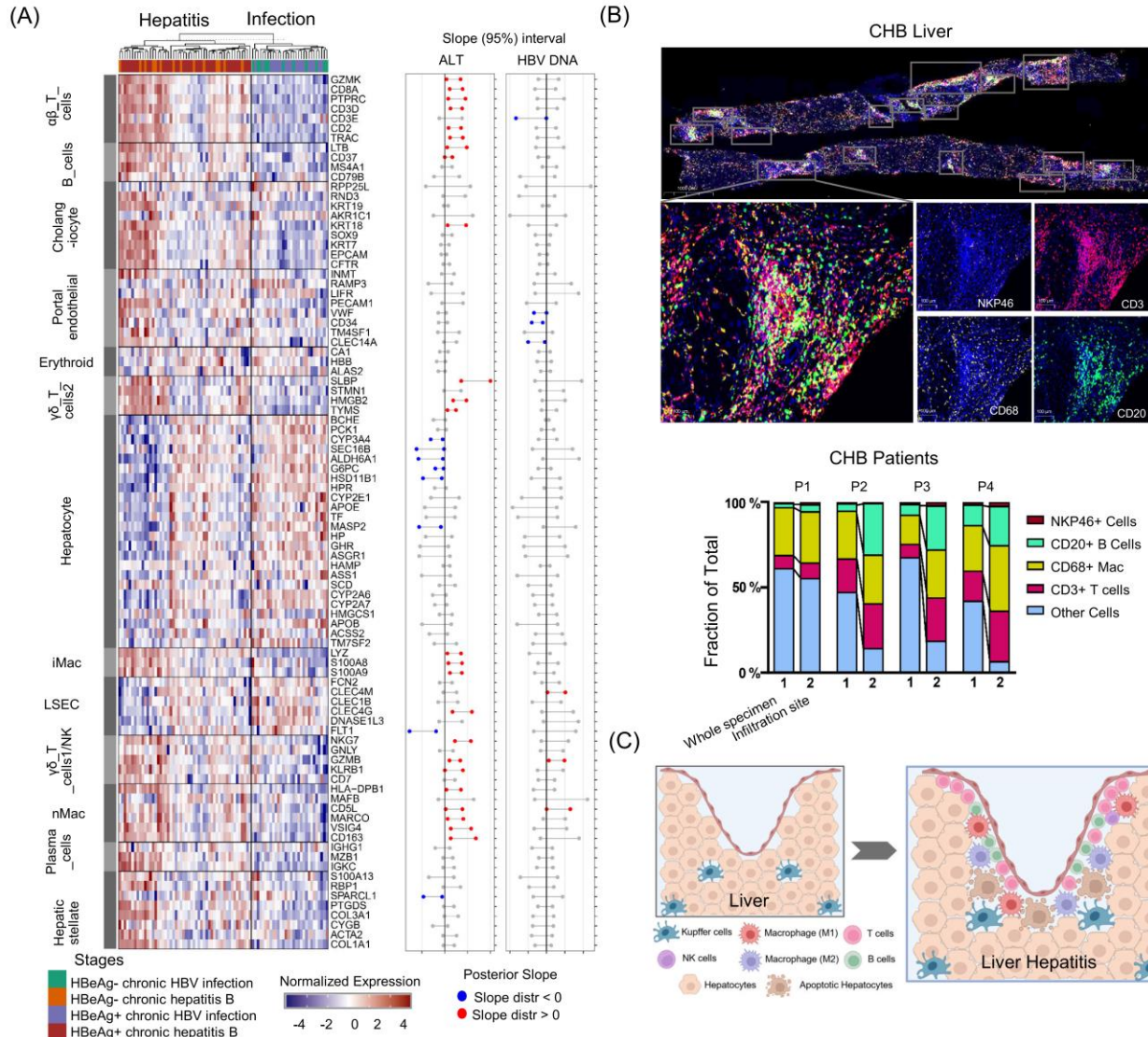


Cell-type specific marker genes in liver based on single-cell RNA-sequencing data.

Results 3

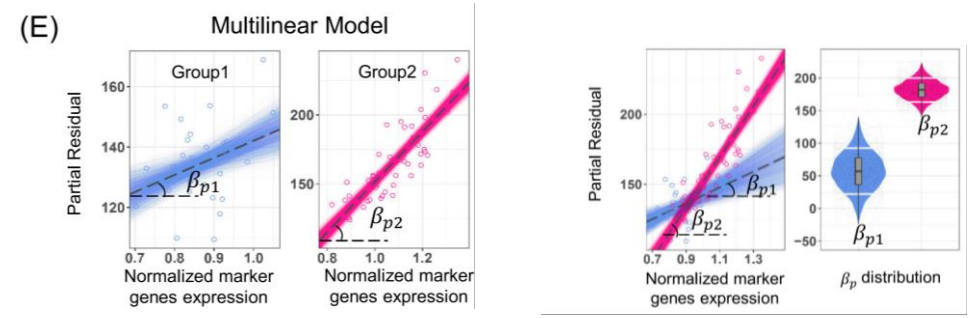
Figure 3

● Immune cell signatures in CHB and their correlation with liver injury



$$(1) \quad y = a + \sum_{p=1}^P x_p f_p \quad \longrightarrow \quad (2) \quad y = a + \sum_{p=1}^P \frac{x_p}{x'_p} y'_p \quad \longrightarrow \quad (3) \quad y = a + \sum_{p=1}^P \beta_p y'_p$$

The a is the background, P is the number of cell types.
 y is one of genes expression in the bulk sample.
 x_p , the expression of the gene if the sample contain only one population p .
 f_p is the fraction of the population p .
 x'_p , the expression of the marker genes if the sample contain only one population p .
 y'_p , the expression of the marker genes in bulk sample.

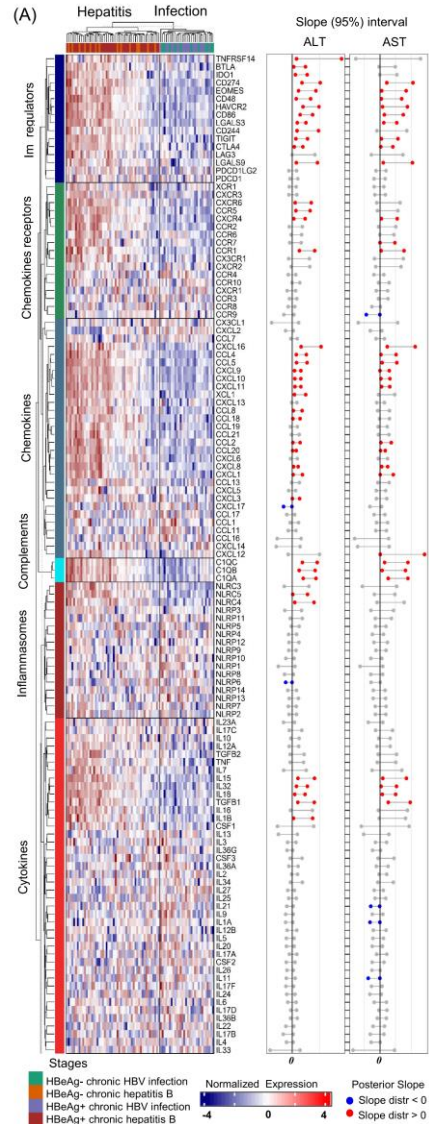


Population-Specific Expression Analysis to deconvolute bulk gene expression into specific cell types during different CHB phases.

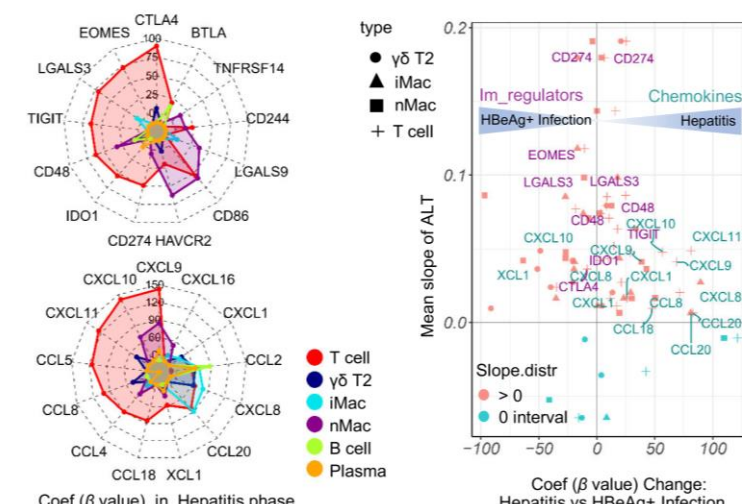
Results 4

Figure 4

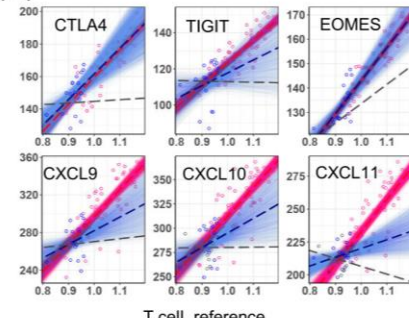
● Immune cell signatures in CHB and their correlation with liver injury



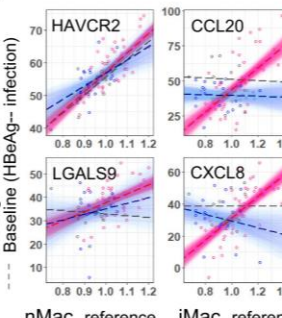
(B) Coefficient (β value) of genes into cell types



(C) Coef (β value) in Hepatitis phase

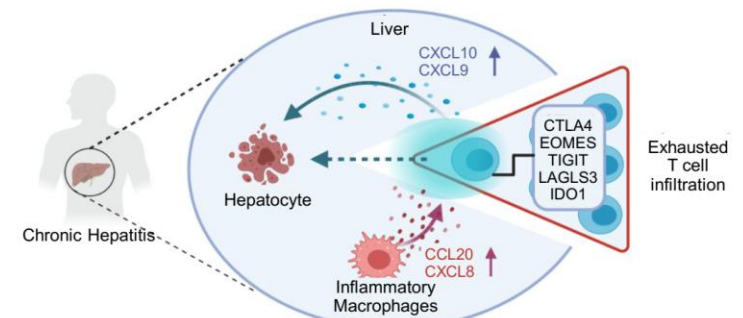


(D)



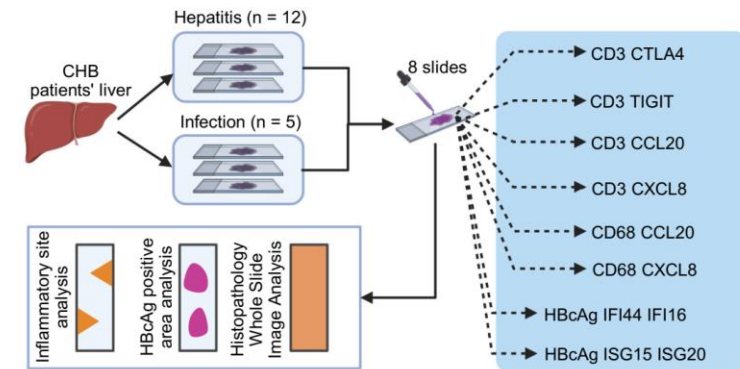
(E)

Potential pathway of exhausted T cell infiltration for hepatocyte injure



(F)

Workflow for Clinical histopathology validation

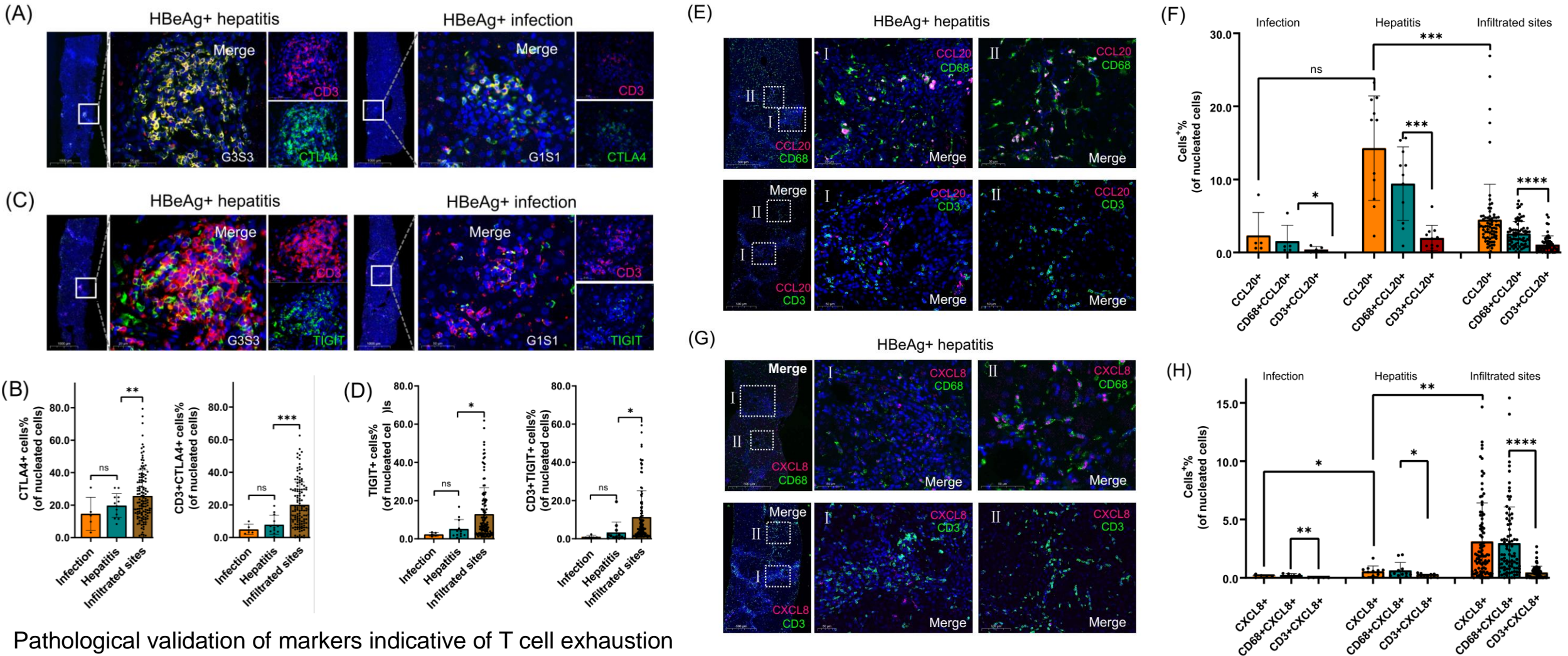


Chemokines and immune-negative regulators in T cells and macrophages associated with liver injury.

Results 5

Figure 5

● Immune cell signatures in CHB and their correlation with liver injury

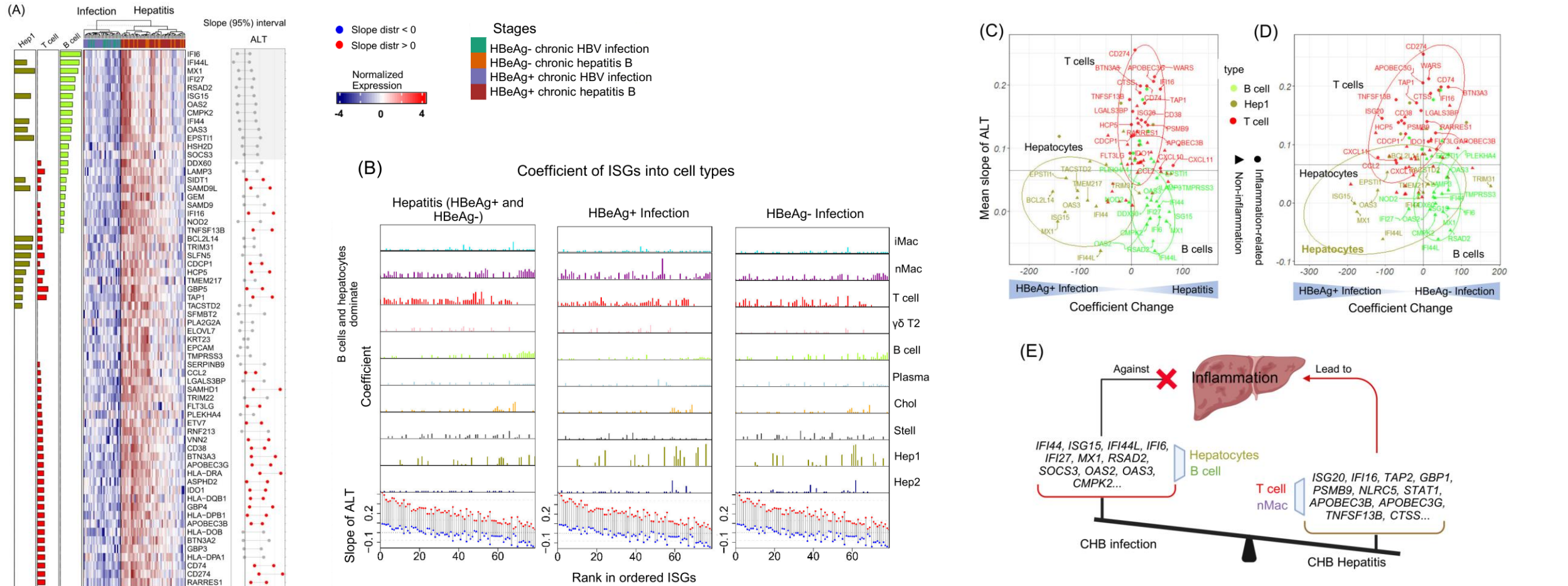


Pathological validation of markers indicative of T cell exhaustion and Chemokines of macrophages activation.

Results 6

Figure 6

● Distinct roles of upregulated interferon-stimulated genes in liver inflammation



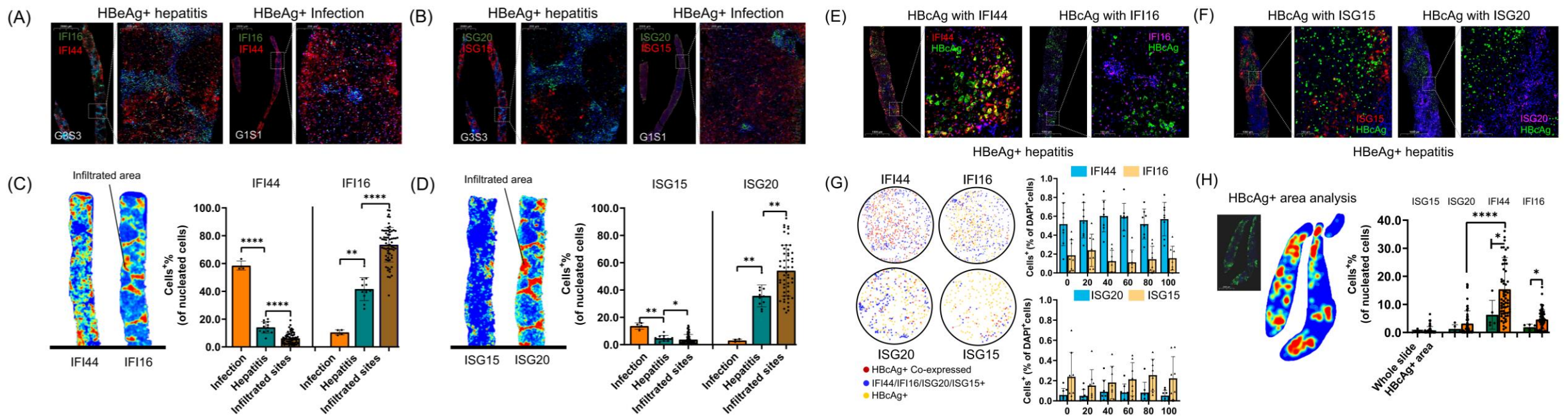
We hypothesized that ISGs primarily expressed by hepatocytes and B cells during the infection phase, exhibited no correlation with ALT levels. Conversely, other ISGs predominantly expressed in T cells and nMacs, and upregulated during the hepatitis phase, showed a positive correlation with serum ALT levels, indicating their involvement in liver injury.



Results 7

Figure 7

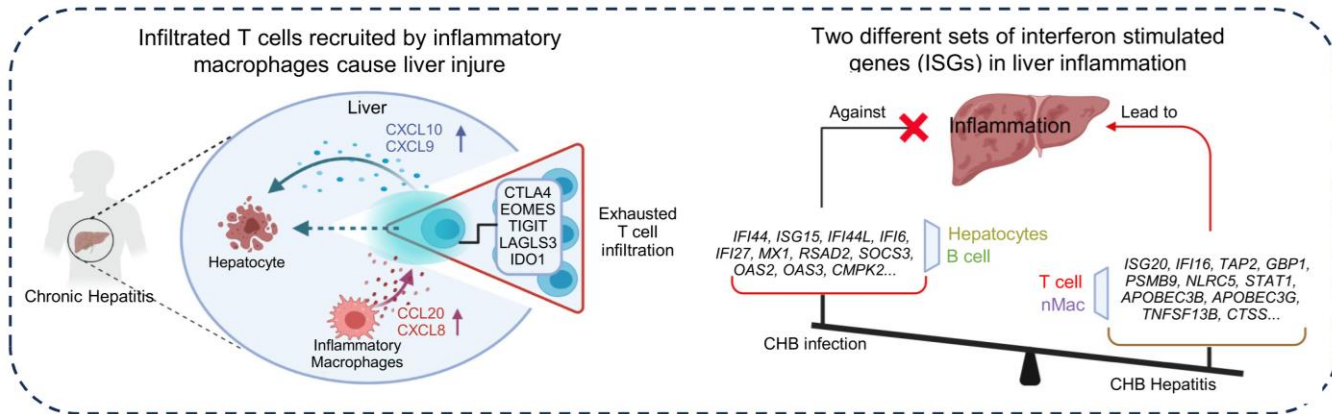
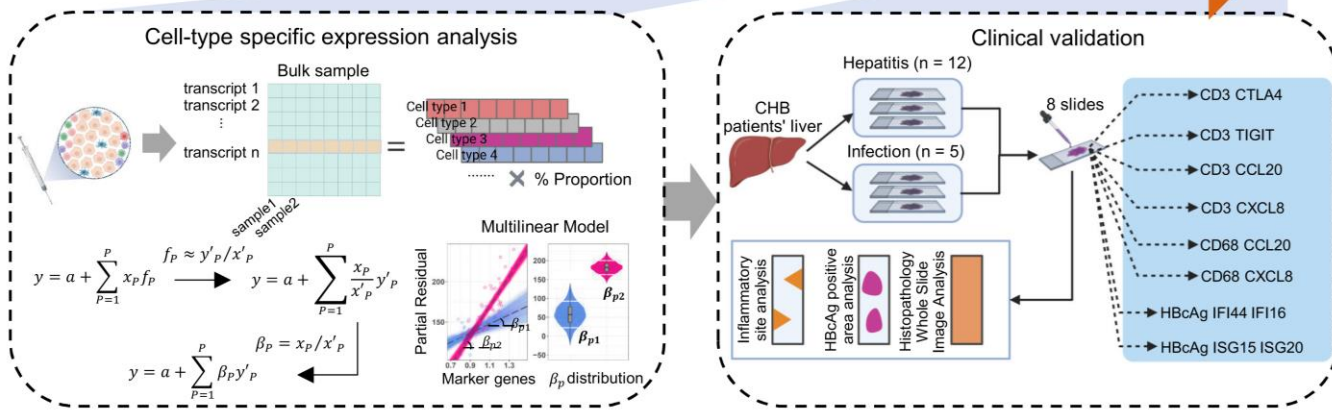
- Pathological validation of distinct cell-type specific interferon-stimulated genes in CHB liver



The results indicated that IFI44 was highly expressed in HBeAg-positive areas, confirming the stimulation of interferon-stimulated genes by the virus across different clinical states.

Summary

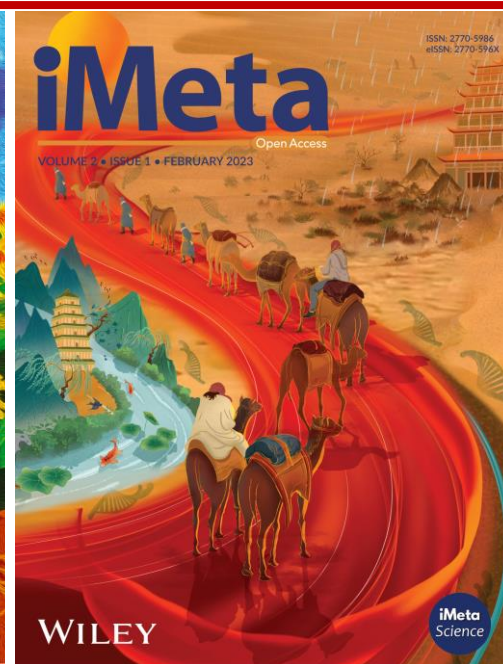
Multi-omics research (bulk transcriptome, single-cell sequencing, clinical parameters)



- This study integrates liver bulk transcriptomic data, single-cell sequencing data, and clinical data to analyze the factors inducing hepatic inflammation in chronic hepatitis B (CHB) from a multi-omics perspective by Bayesian regression.
- Macrophages secrete chemokines like CCL20, CXCL8 to recruit immune-exhausted T lymphocytes (CTLA4, TIGIT) into liver tissue.
- Innate immunity within hepatocytes is suppressed, impeding interferon-stimulated genes (ISGs) from initiating antiviral effects.
- Activation of innate immune pathways in infiltrating T cells and macrophages further exacerbates inflammation formation.

iMeta: Integrated meta-omics to change the understanding of the biology and environment


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