Natural history of HBV disease

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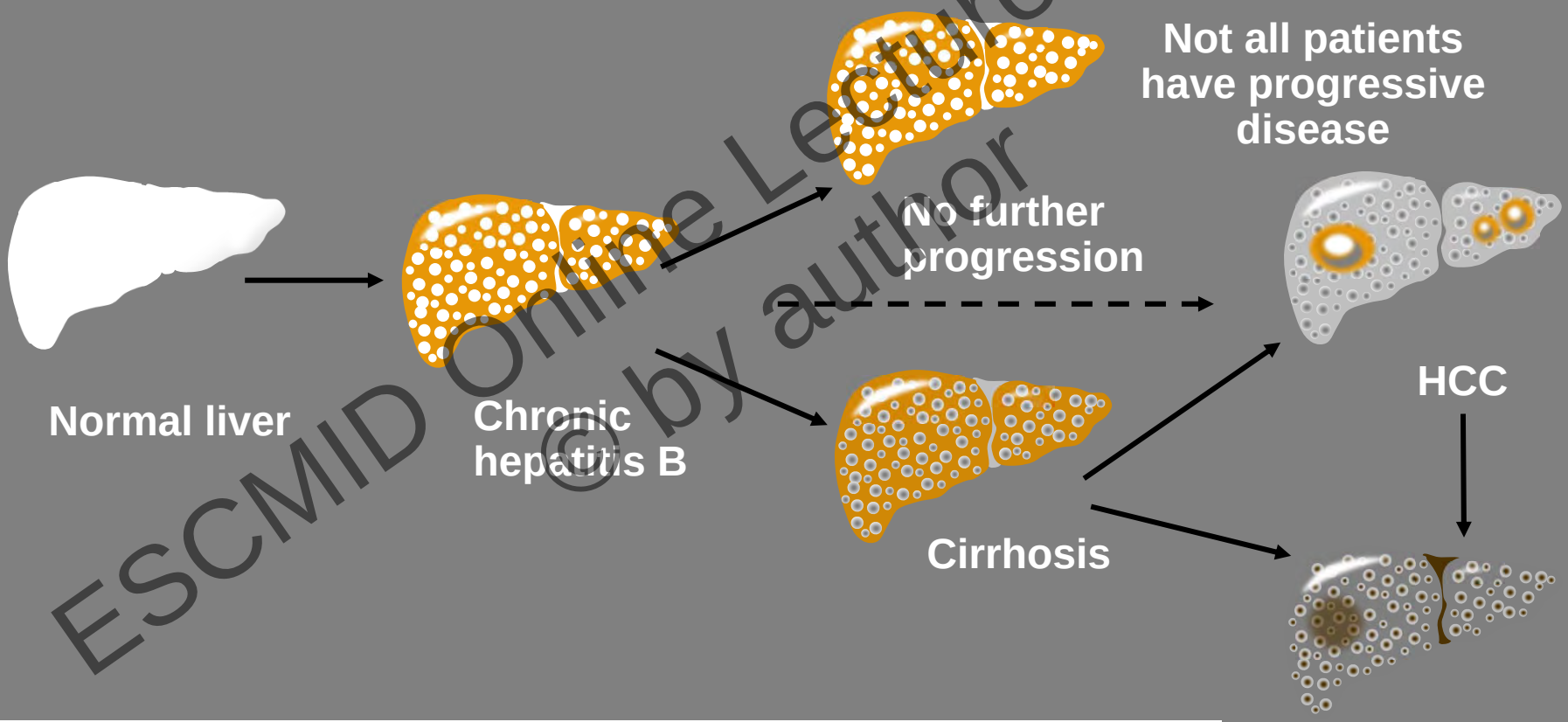
Challenges in the Management of Viral Hepatitis, ESCMID Postgraduate Education Course
14 - 15 October 2016, Cavtat, Croatia

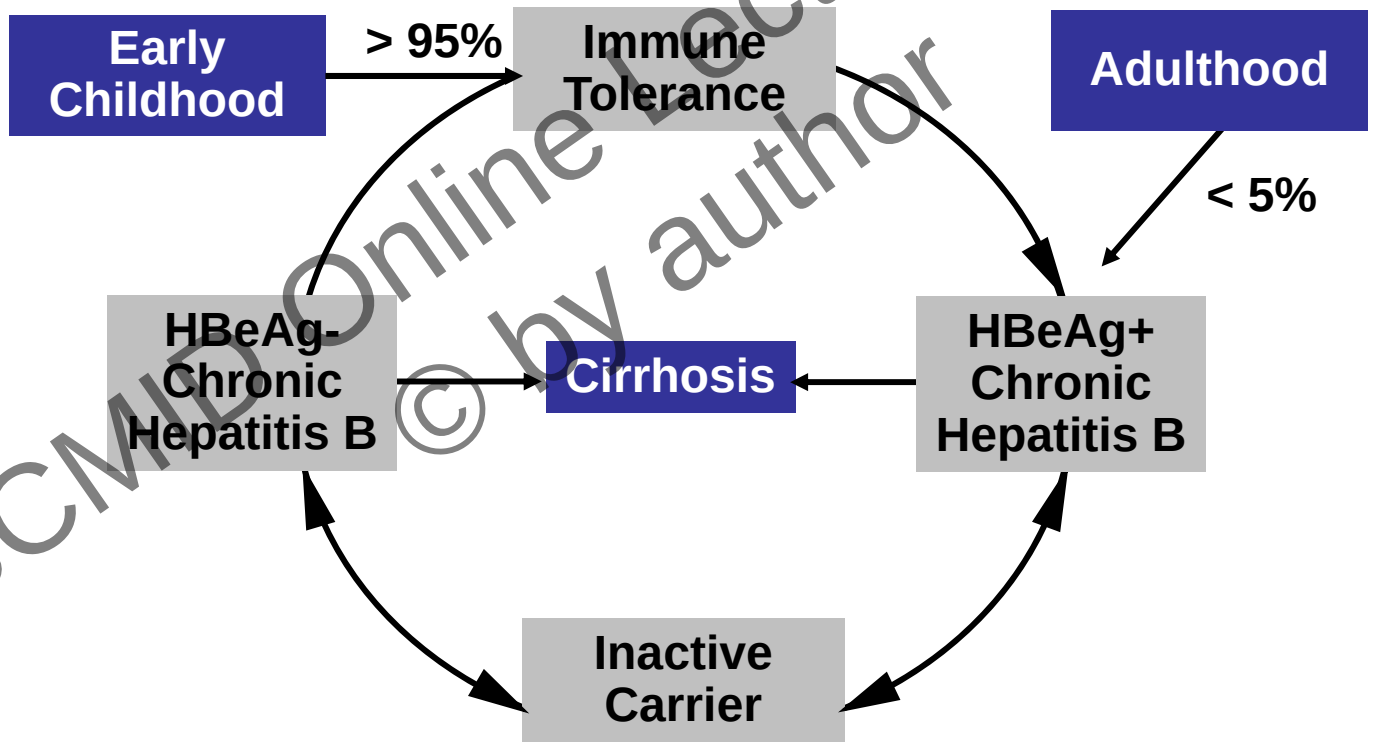
Natural History of Chronic Hepatitis B



Approximately 15% to 40% of chronic hepatitis B patients will progress to cirrhosis, HCC, or liver failure

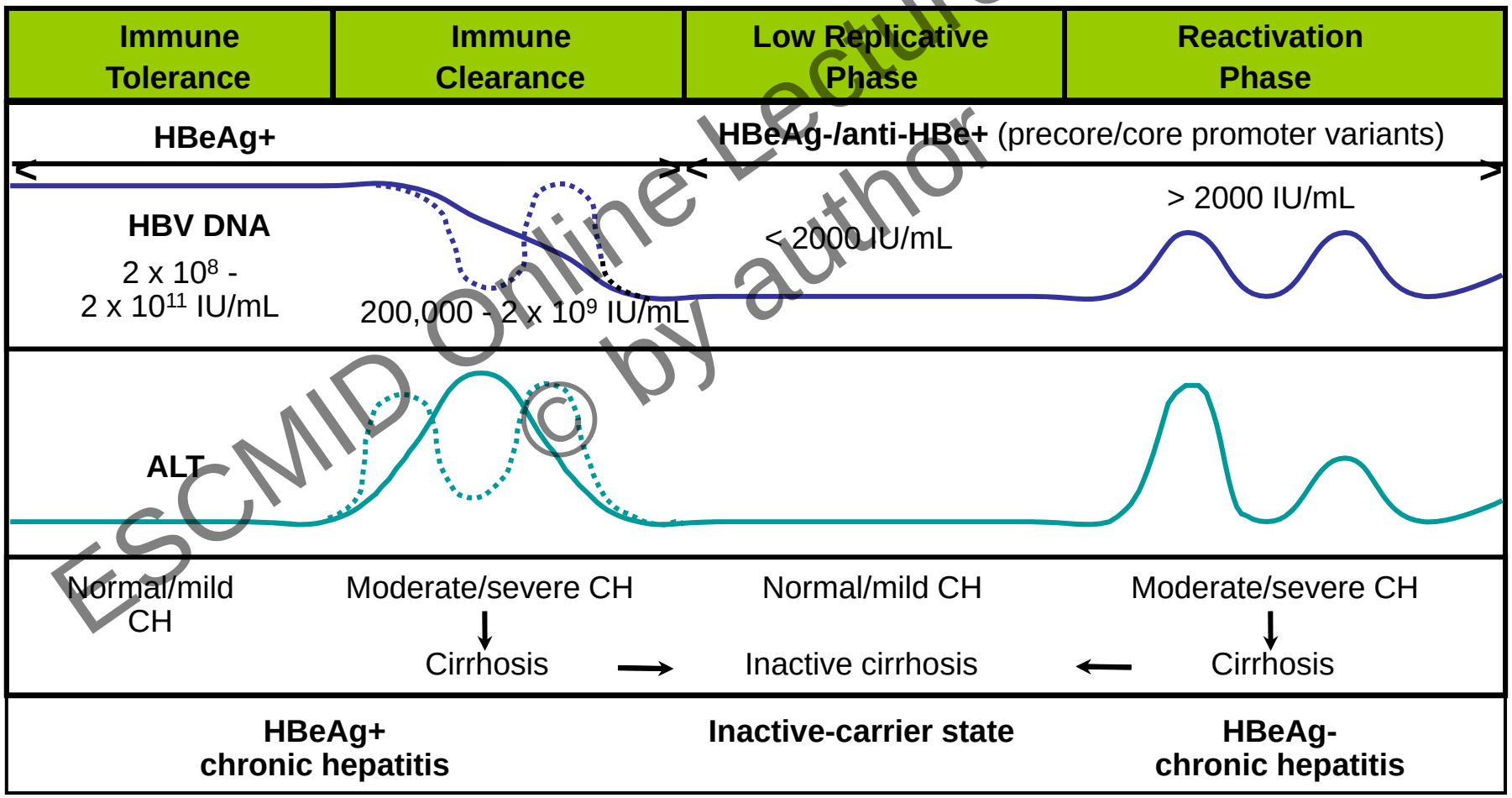
EASL. J Hepatol. 2012;57:167-185. Clinical Care Options

Natural History of HBV Infection



Slide by W. Ray Kim, Clinical Care Options, Chen DS, et al. J Gastroenterol Hep. 1993;8:470-475., Seeff L, et al. N Engl J Med. 1987;316:965-970.

Phases of Chronic HBV Infection



Slide by A. S. F. Lok, Clinical Care Options

Hepatitis B virus

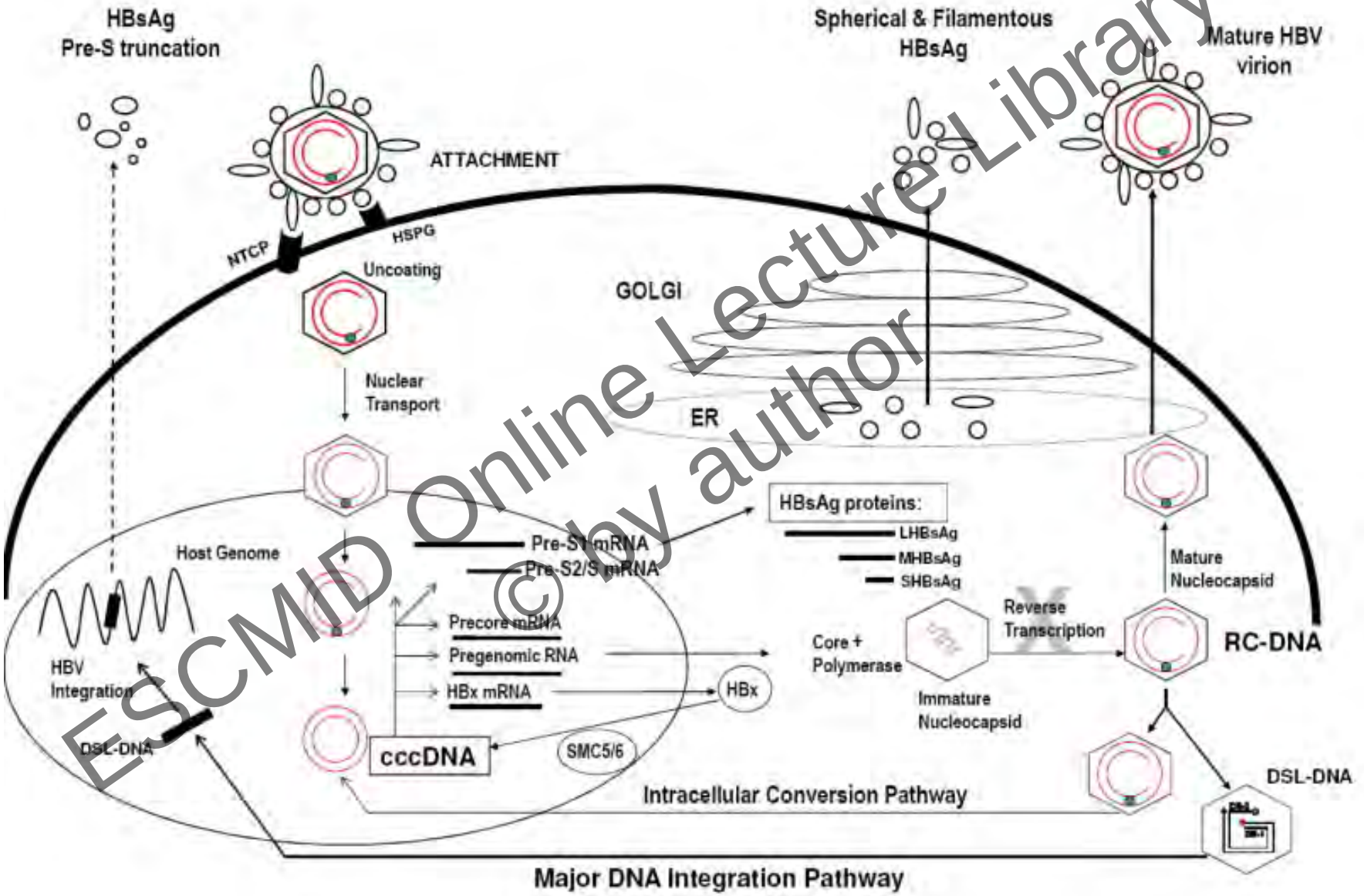
- **Taxonomy:**
- Family: *Hepadnaviridae* (hepatotropic DNA viruses)
- Genera: Orthohepadnaviruses (infect mamals, human, woodchucks, ground squirrel etc.)

- **Genome:**
- relaxed, circular, partial double-stranded DNA (3.2 kb) with asymmetric strands
- higher mutation rate than other DNA viruses ($1.4\text{-}5x10^{-5}$ base substitutions per site per year)
- highly overlapping genome
- replicates via reverse transcription of an RNA intermediate

- **Hallmark of the establishment of infection:**
- Formation of covalently closed circular cccDNA that persists within the nucleus of infected hepatocytes

Datta et al, J Clin Exp Hepatol 2012;2:353-365

Figure 2



Sodium taurocholate cotransporting polypeptide, NTCP; Cornberg et al. 2016.

Persistence of cccDNA is the major obstacle to viral eradication (sterilizing cure)

Treatment	Mechanism of action	Specific cccDNA degradation	Killing of infected hepatocytes
NA	Inhibition of HBV polymerase	No	No
IFN-α	Immune modulation Inhibition of HBV replication - Epigenetic regulation of the transcriptional activity of cccDNA - Upregulation of APOBEC activity leading to cccDNA hypermutation and degradation	Yes (in a high dose)	Yes (indirectly in some patients)
LTβR agonist	Upregulation of APOBEC3B activity for cccDNA hypermutation and degradation	Yes	No
Adoptive T-cell therapy (T-cells expressing chimeric antigen receptor)	T cell immune response against HBV-infected hepatocytes	No	Yes
Genome editing tools (ZNFs, TALENs, CRISPR/Cas9)	Site specific cleavage of cccDNA	Yes	No

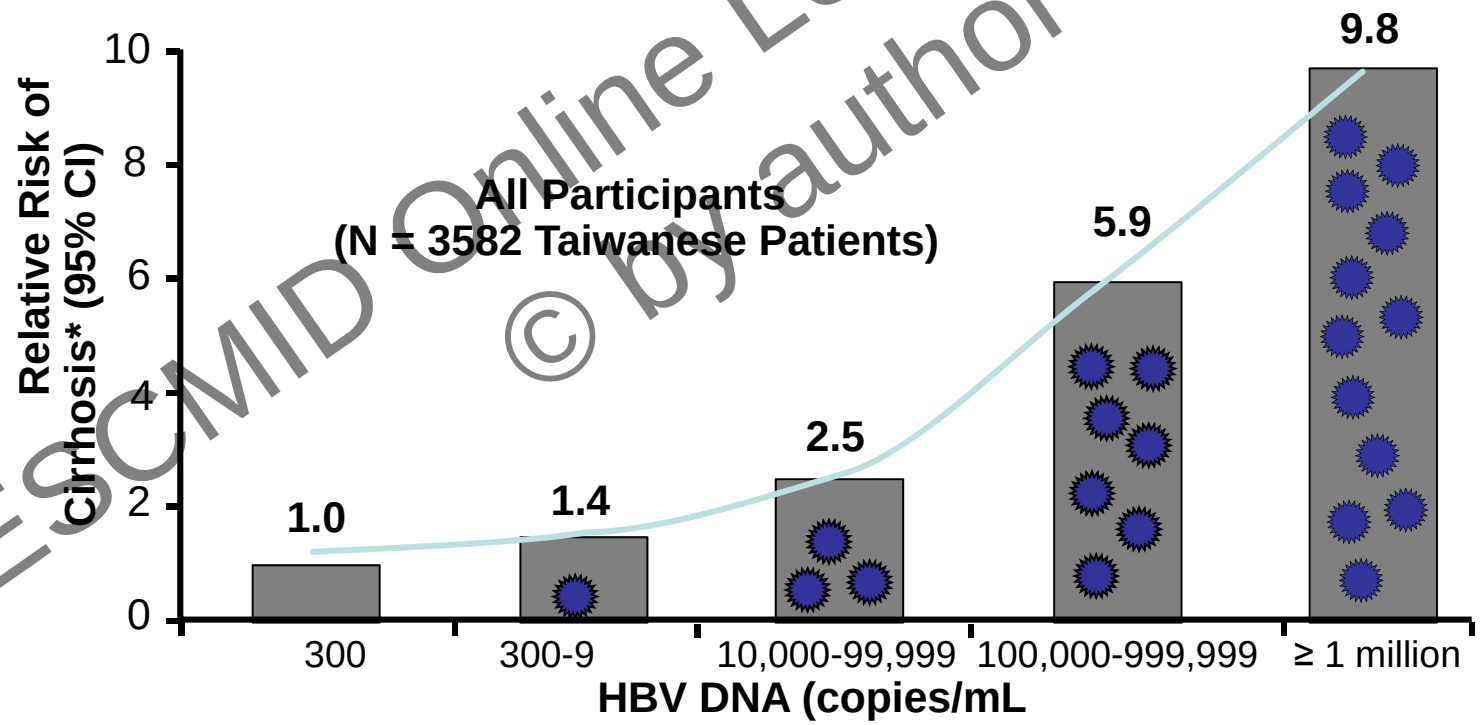
Determinants of the natural history in chronic hepatitis B

- **Virological determinants**
- HBV DNA
- HBV genotypes
- mutants

- **Host (immunity)**
- Single nucleotide polymorphisms (SNPs) in genes coding for pattern-recognition receptors
- SNPs of cytokine genes
- HLA genes

REVEAL: **Serum HBV DNA** level is significantly and independently associated with the incidence of cirrhosis, HCC and liver-related mortality

- Serum HBV DNA ~ 2000 IU/mL (≥ 10^4 copies/mL) is an independent predictor of cirrhosis development
- HBV genotype and basal core promoter A1762T/G1764A mutants as well as precore G1896A mutants were shown to be predictors of HCC risk.



5. Iloeje UH, et al. Gastroenterol. 2006;130:678-686.

HBV genotypes	Number of subgenotypes	Geographic distribution
A	7	North America, northern Europe, India, and Africa
B	9	Asia
C	12	Asia
D	7	Southern Europe, Middle East, and India
E		West Africa and South Africa
F	4	Central and South America
G		United States and Europe
H		Central America and California
I		Vietnam
J		Japan

Datta S, et al, 2012;2:353-365; Fung SK, et al. 2004;40:790-792. Norder H, et al. Intervirology. 2004;47:289-309. Tran TT, et al. J Virol. 2008;82:5657-5663. Tatematsu K, et al. J Virol. 2009;83:10538-10547.

Table 4 Comparison of clinical features among different HBV genotypes

Acute infection: chronicity rate	A>D; C>B (C2>B1; C2>B2); A>C>B
Acute infection: rate of fulminant hepatitis	D>A; B>C (B1>C2)
Length of HBeAg+ phase of infection	A>D; C>B (by 10 yrs); C>A, B, D, F
Emergence of HBeAg-negative mutation	D>>A
Emergence of core promoter mutations	A>D; C>B
Response to interferon therapy	A>D: B>C
Age of HCC development	B2 earlier than C2; F earlier than A, C, D
Lifelong HCC risk	C2>B2; F>D

Tong S et al. Emerging Microbes Infect, 2013

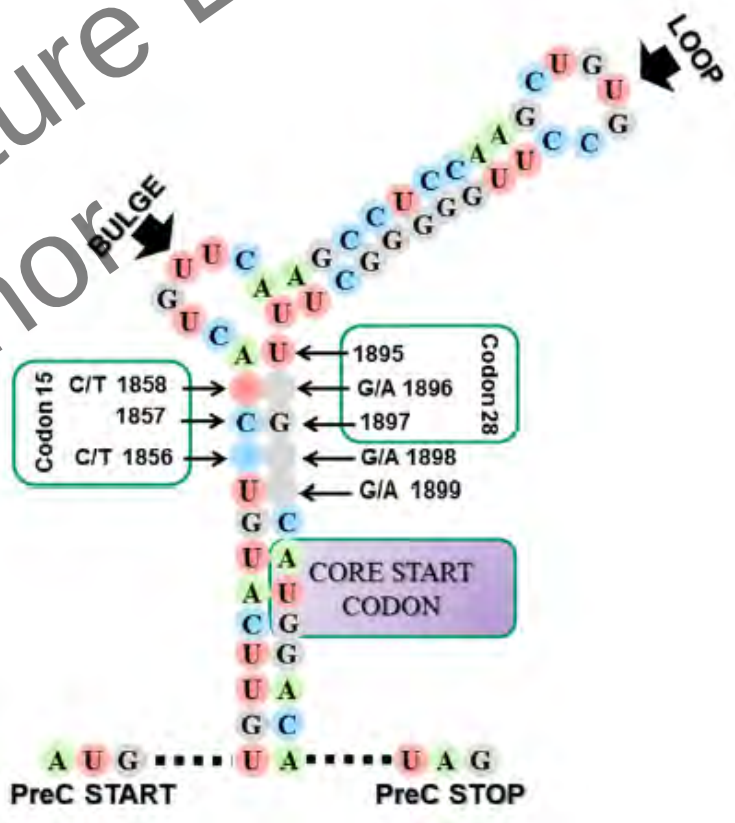
Biological and clinical significance of mutants in the natural history of chronic HBV disease

- Pre-core region mutations (PC mutation G1896A) and Basal core promoter region mutations (BCP mutations A1762T/G1764A) associated with the reduction or loss of HBeAg synthesis at translational and transcriptional levels
- Insertions or deletions in the preS1, preS2 and S regions
- Substitutions in the „*a*" determinant of the HBsAg
- Mutations in the X gene
- Resistance-associated mutations in the *pol* region

Yang et al. J Natl Cancer Inst 2008;100:1134-1143; Kao JH, et al. Gastroenterology 2003;124:27-334; Chou YC, et al, Gut 2008;57;91-97; Fang ZL, et al, Am J Gastroenterol 2008;103;224-2262; Wu CF, et al. Carcinogenesis 2008;2:106-112; Yuan JM, et al. Cancer Epidemiol Biomarkers Prev 2009;18:590-594. , Caligurei P et al. WJG 2016;22:145-154

Pre-core mutation

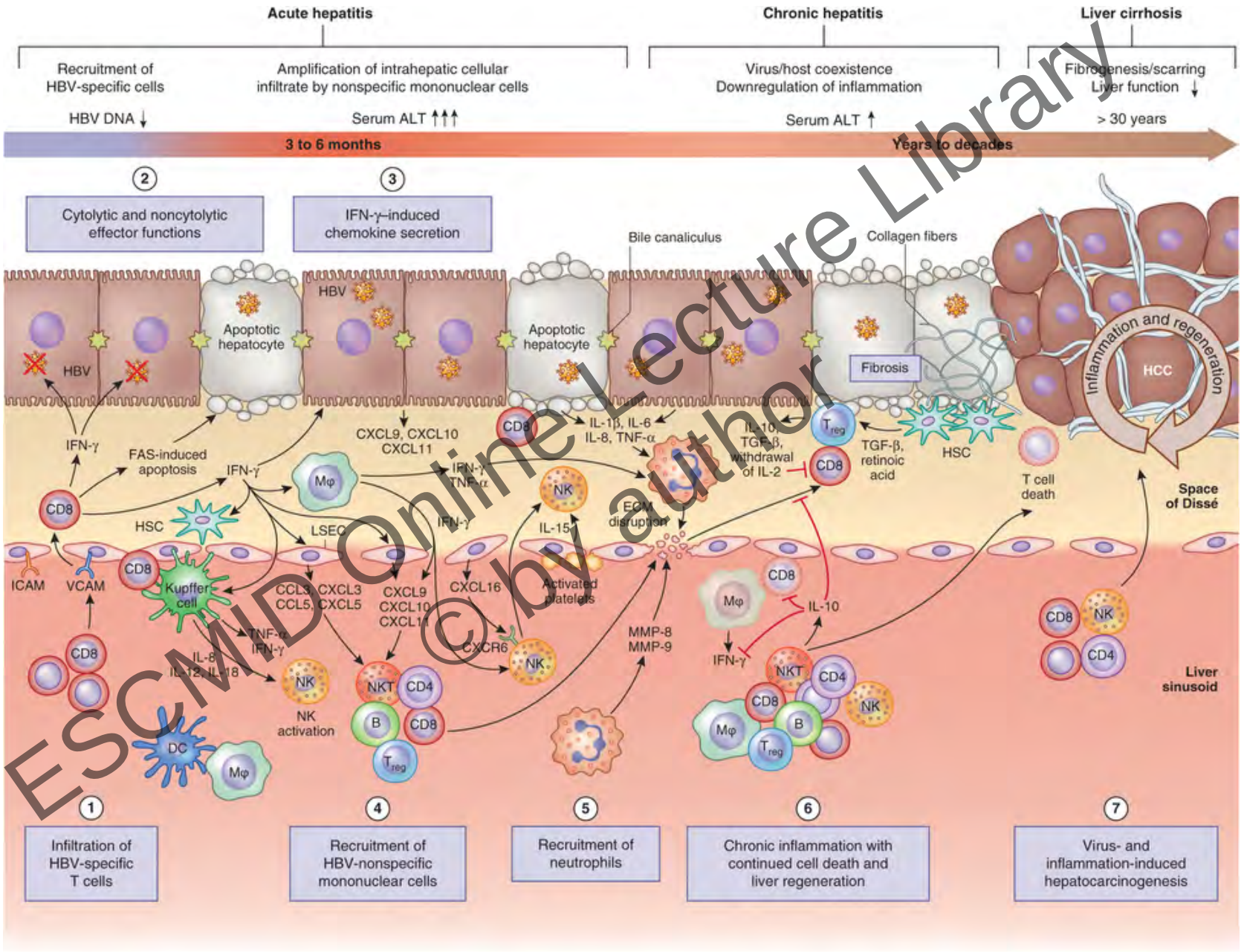
- **G1896A** converts the 28th codon of HBeAg from Tryptophan to translational stop codon (TGG to TAG) and decreased HBeAg synthesis
- Occurence of G1896A mutation is genotype specific:
- Genotypes A, C1, F2 and F3 with 1858C pair with the 1896G (wild type)
- Other genotypes (D, B, E, H, F, G) with 1858T pair with the 1896A (HBeAg mutants)



Epsilon structure of the pre-core gene coding for HBeAg

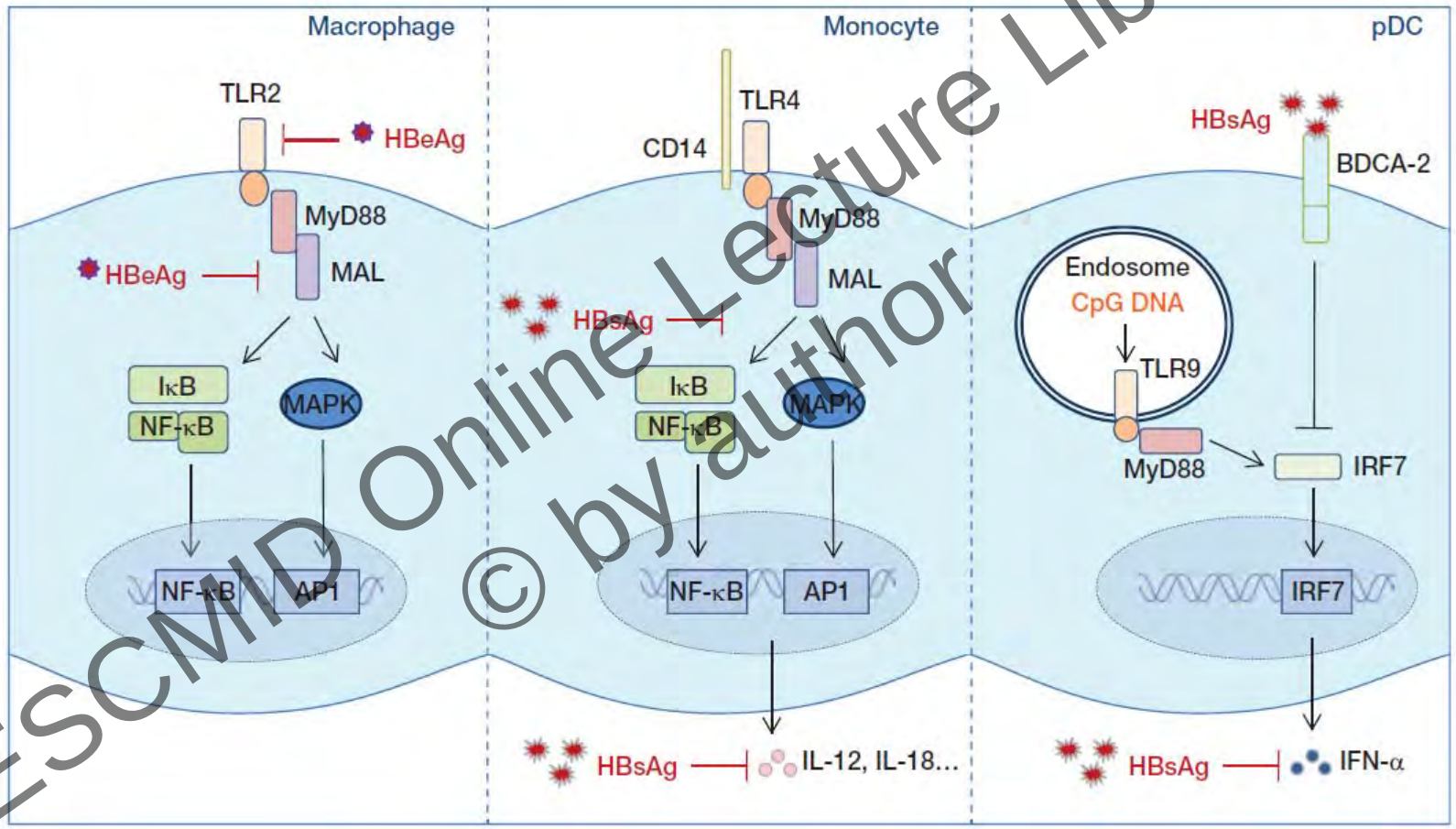
Datta S, et al, 2012;2:353-365

Host determinants of the natural history of chronic hepatitis B



Reherman B. Nature Med 2013;**19**,859–868.

Figure 3. HBV impairs function of immune cells



Revil P and Yuan Z. Antiviral Therapy 2013;18:1-15.

Host factors (immune system)	Clinical relevance
TLR5 rs5744174 and C allele and TLR9 rs5743836	Earlier spontaneous HBeAg seroconversion
TLR5 rs5744174	Higher IFN-γ synthesis in chronic infection
G allele at TLR5 rs4986790	Associated with spontaneous HBsAg seroconversion
A allele of IL-10 SNP rs1800872 and G-allele of IL-12β SNP rs3212217	Predictors of spontaneous HBsAg seroconversion
IL-10 – 1082 G/G genotype and IL-12β – 10993 C/G genotypes	Earlier spontaneous HBeAg seroconversion
HLA-DR2, HLA-DR*0406, HLA-DR7	Protective role in acute HBV infection
HLA-DRB1*1301-02	Protection against persistent HBV infection (Gambia, Germany, Korea)
Furin	Intrahepatic IFN-γ mediated suppression of furin reduces HBeAg biosynthesis
Program Death 1 (PD-1) and PD-L1	IFN-γ enhances the PD-1 expression to reduce CTL activity and avoid excessive hepatocyte damage

WU J-F and Chang M-H. J Biomed Sci 2015;22-29

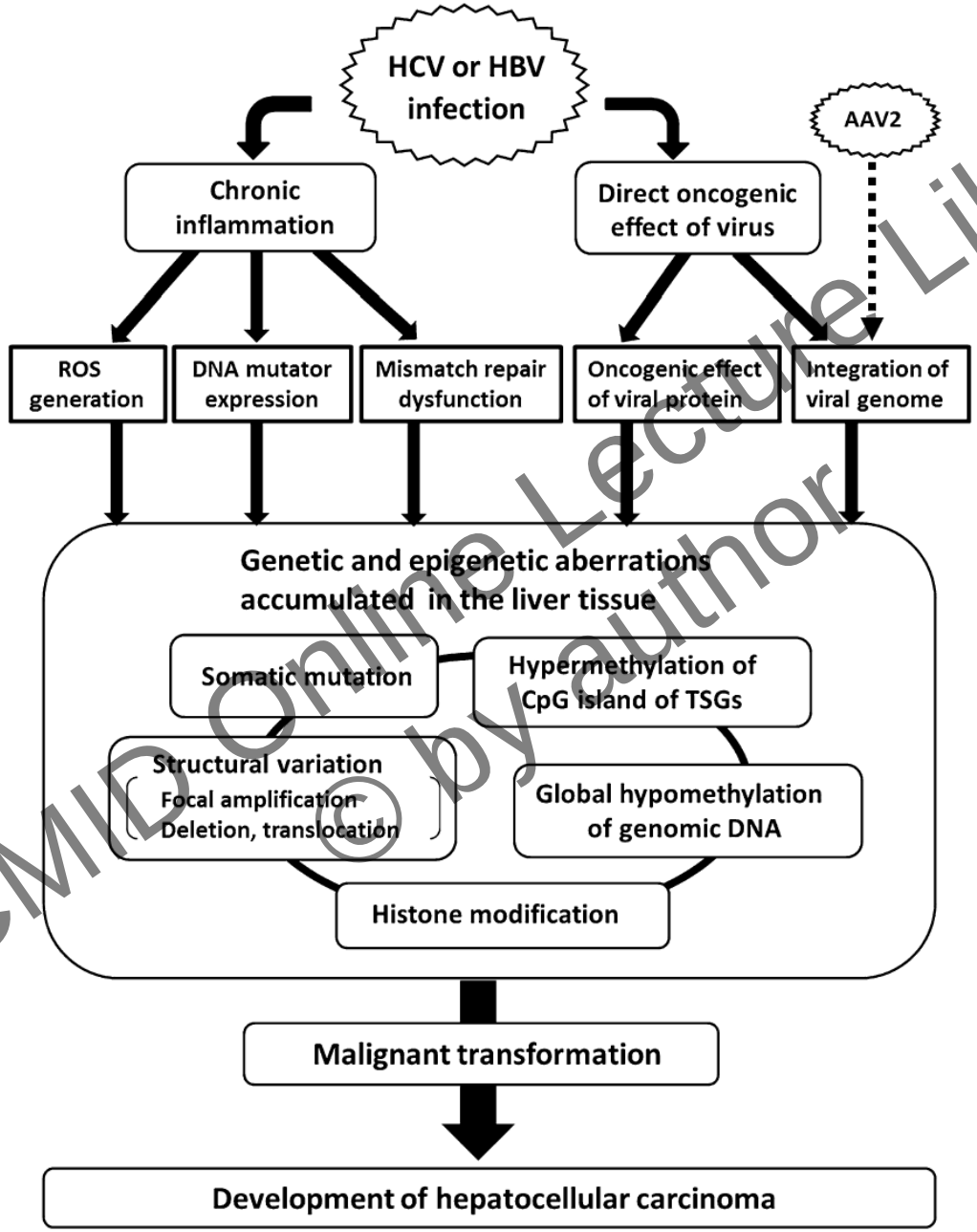
HBV and hepatocellular carcinoma

- HBV infection is the main risk for the development of HCC in Asian-Pacific region and Africa

- **Predictors of hepatocellular carcinoma:**
  - Intensive viral replication (HBV DNA)
  - HBeAg and genotype C
  - HBV mutations (preS mutations in the genotype C)

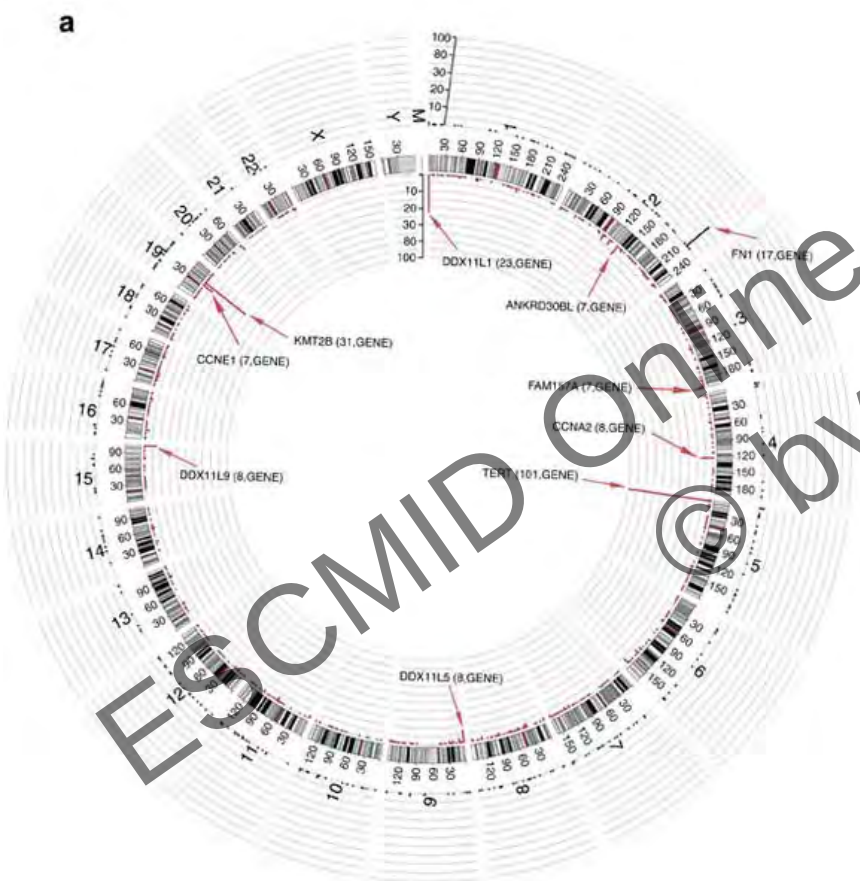
- Hepatocellular carcinoma can develop at any stage during the natural history of chronic HBV disease, e.g. in HBV-infected liver lacking active inflammation and liver damage/fibrosis

Takeda et al, J Gastroenterol, 2016



Takeda et al, J Gastroenterol, 2016

HBV integration and oncogenic transformation



- Integration of HBV DNA into the host genome causes genetic damage and chromosomal instability
- HBV integrates into rare fragile sites and functional genomic regions including CpG islands
- The most common HBV integration event is located at the telomerase reverse transcriptase gene (*TERT*)
- distinct pattern in the preferential sites of HBV integration between tumour and non-tumour tissues

Distribution of integration breakpoints across the human genome in 426 paired HCC samples. Each bar represents the sample frequency of HBV integration breakpoints at a particular locus in the human genome (hg19). Tumour (red) and non-tumour (dark blue) samples with HBV integrations are shown on the inner and outer circles, respectively.

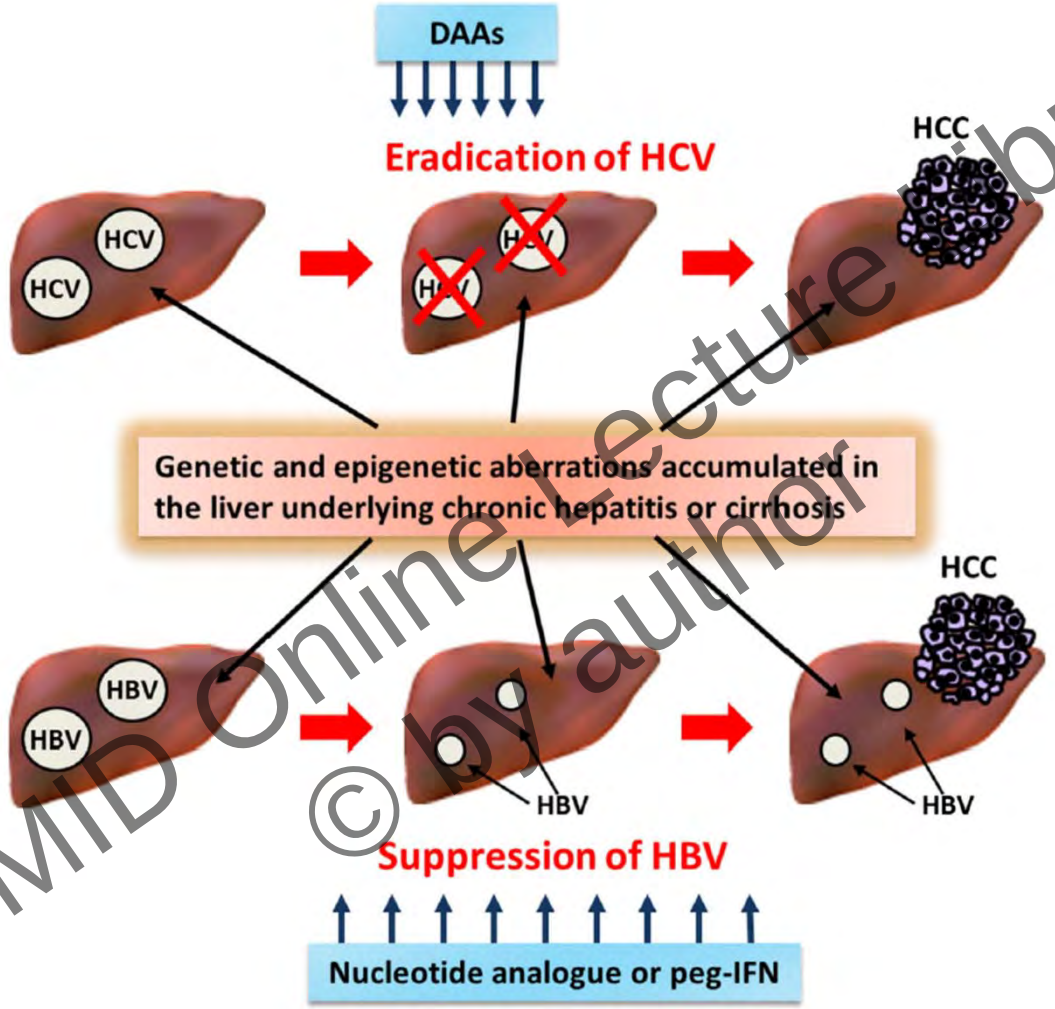
Zhao LH, Nature Communications, 2016

HBV oncogenic proteins

- **HBV X protein**
- Transactivation of host and viral genes
- Stimulation or inhibition of various signal transduction pathways
- C-terminal domain of HBx binds to the p53 in the cytoplasm and in part prevents its nuclear entry and ability to induce apoptosis (contribution to early stages of HCC development)

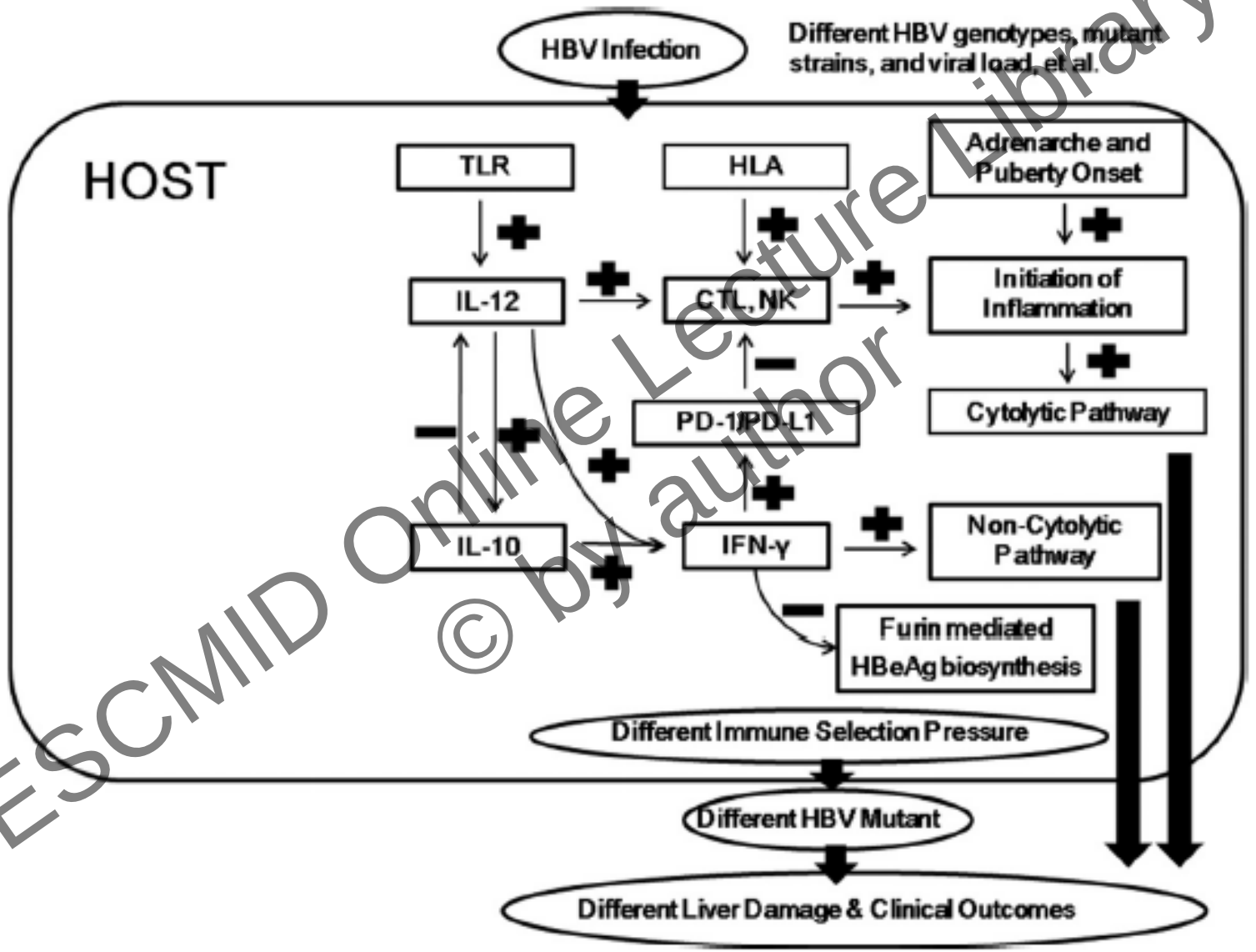
- **Truncated and mutated PreS1/preS2/S proteins (LHBsAg and MHBsAg)**
- Transactivation of transcription factors
- Stimulation of oncogene promotors
- Modulation of cyclins and cyclin kinases

Takeda et al, J Gastroenterol, 2016; Li YW et al., WJG 2016;22:1943-1952.



Accomulation of abberations strongly suggests that chronically damaged liver tissue has a significant malignant potential, even after eradication or suppression of hepatitis viruses

Takeda et al, J Gastroenterol, 2016



WU J-F and Chang M-H. J Biomed Sci 2015;22-29

Conclusion

- Recent advances in molecular virology and immunology had a significant contribution to knowledge on the natural history of HBV infection

- The course of the natural history of HBV disease is determined by complex interactions between the virus and the host