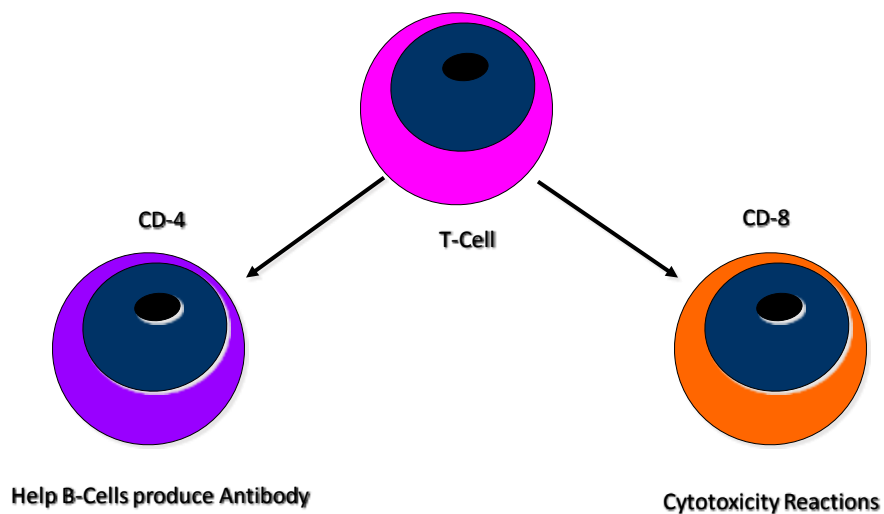


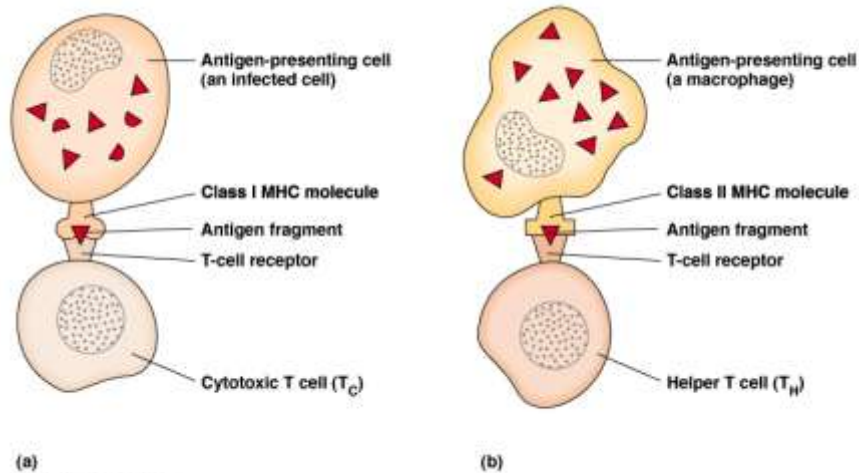
Immunological Mechanisms in OBI

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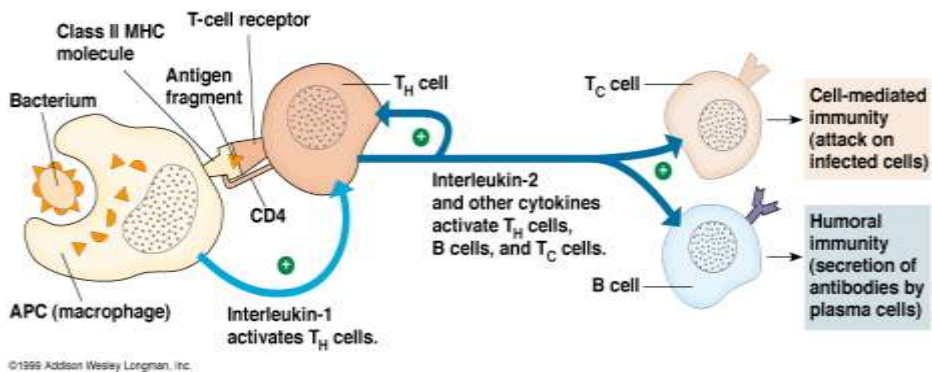
T-Cell Subpopulation



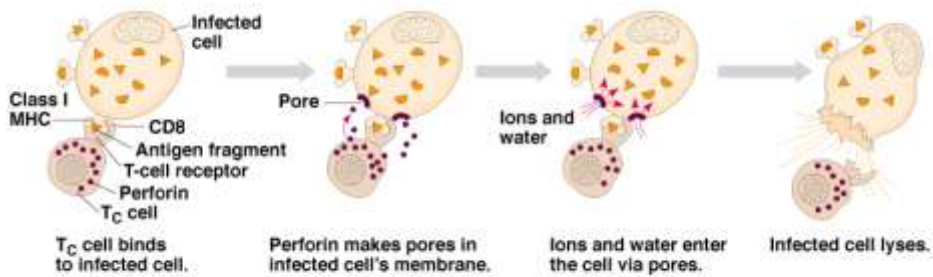
T Cells Only Recognize Antigen Associated with MHC Molecules on Cell Surfaces



Central Role of Helper T Cells

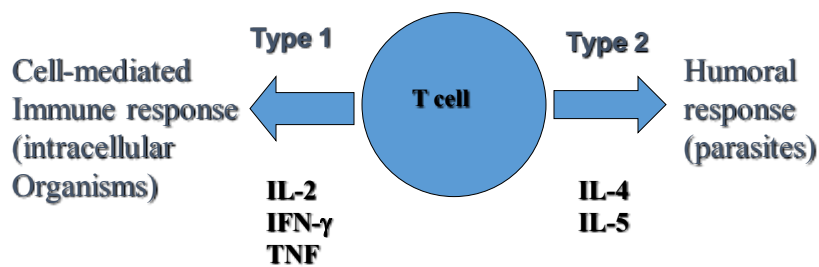


Cytotoxic T Cells Lyse Infected Cells

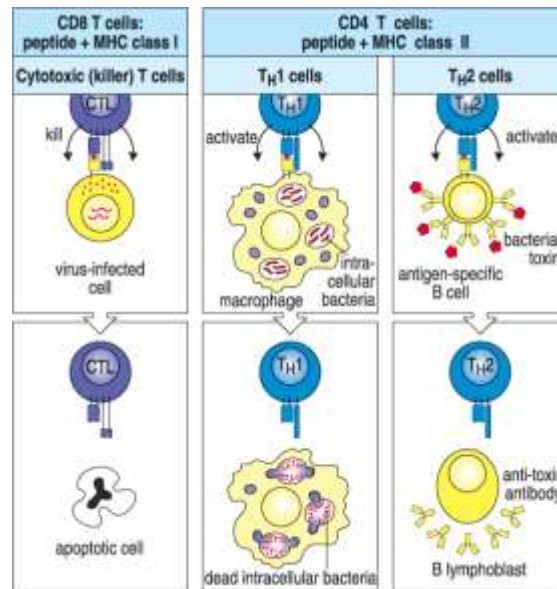


(a)
©1999 Addison Wesley Longman, Inc.

Cytokine secretion and biological activities of T_H1 and T_H2 Subsets



Effector T Cells



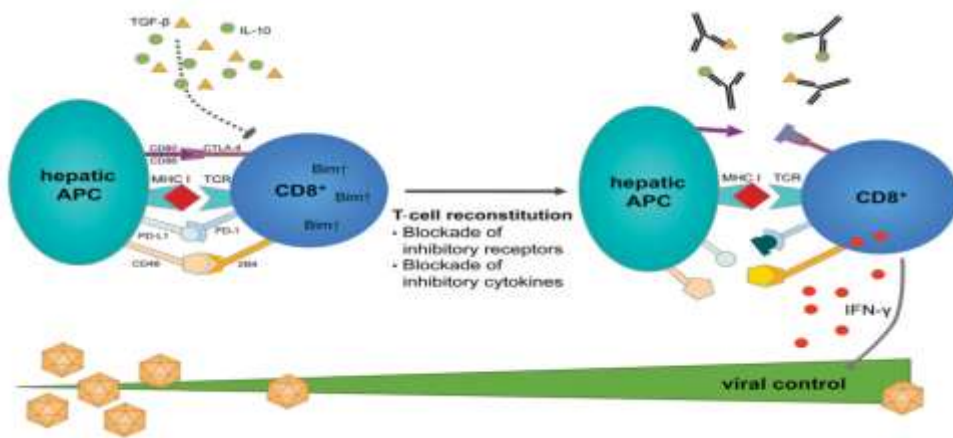
Immune Response to Viruses:

- (i) production of type I IFN
- (ii) killing of infected cells via NK
- (iii) production of pro-inflammatory cytokines and chemokines that contribute to the maturation and recruitment of adaptive immune responses

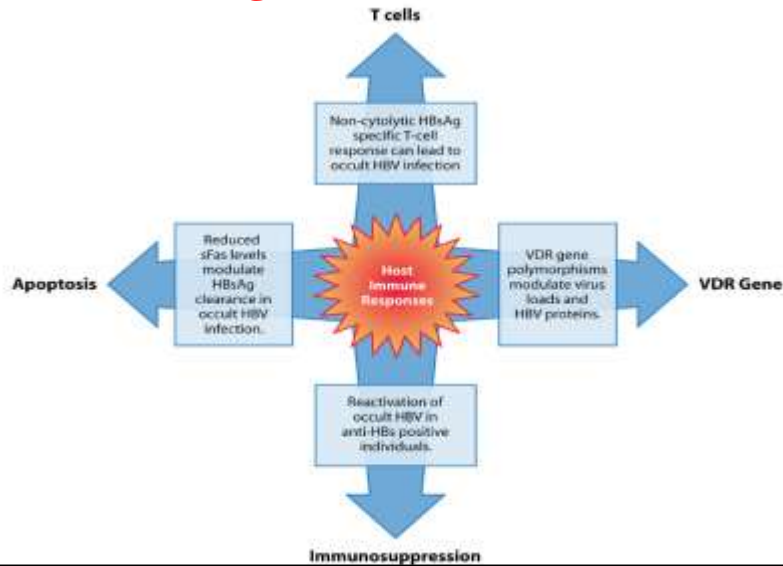
NK cell and T cell response at various stages of HBV infection

	HBV	
	Acute/resolving	Chronic
NK cells	Suppressed during peak viraemia	Impaired IFN γ production, hypercytolytic
CD4 ⁺ T-cells	Multispecific and vigorous	Weak, monospecific, dysfunctional
CD8 ⁺ T-cells	Multispecific and vigorous	Weak, monospecific dysfunctional,

CD8⁺ T-cell mediated viral control might be achieved by (i) blockade of co-inhibitory receptors such as PD-1 or 2B4 and (ii) blocking inhibitory cytokines such as TGF- β or IL-10.



Host immunological responses leading to occult HBV infection



- Lower soluble Fas (sFas) in OBI than in chronic HBV infection
- *The Fas expression system is known to modulate apoptosis of infected hepatocytes and also plays a key role in the removal of aged hepatocytes and maintenance of normal liver homeostasis.*
- Lower sFas levels in OBI indicates decreased apoptotic inhibition in OBI and could be one of the mechanisms for clearance of HBsAg and downregulating HBV replication in OBI
- Reduced expression of CXCL12, a chemokine that modulates apoptosis, may play a role in OBI

- Differences in the HBV-specific cell-mediated immune response have been described in OBI
- Anti-HBc positive in Occult HBV patients had T-cell responses concurrent with protective memory, while anti-HBc-negative occult HBV patients had inadequacies in maturation of protective memory
- A noncytolytic HBsAg-specific T-cell response has been suggested as the potential mechanism for OBI associated with very low and undetectable levels of HBsAg

- Vitamin D3 and the VDR regulate several cytokines and are important determinants of the anti-HBV response
- Polymorphisms in the VDR gene have been linked to the outcome of OBI
- Differences in HBV DNA levels and loss of HBeAg have been linked to certain VDR genotypes
- Polymorphisms in the VDR gene have been detected in occult HBV infections .

Illustration of the effects of cytokines on each other. Serum levels of IL-10 and IL-17 were increased in OBI patients; hence, production of IL-12 and SDF-1 α was decreased

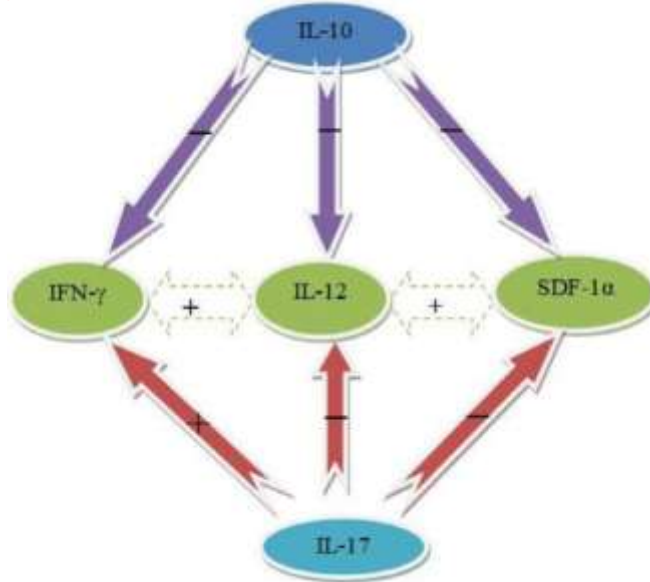


TABLE 1. Serum levels and polymorphisms of cytokines and chemokines among OBI patients*

Evaluated immunologic factor	OBI patients	Healthy clearance controls	p value	References
Serum levels of cytokines and chemokines (pg/mL)				
IL-10	15.05 ± 1.1	10.2 ± 1.0	<0.001	Arababadi et al. ¹¹
IL-17	12.48 ± 2.00	4.43 ± 0.54	<0.001	Arababadi et al. ¹¹
IL-12	4.06 ± 0.53	5.34 ± 1.11	>0.1	Arababadi et al. ¹⁶
IFN- γ	9.26 ± 0.8	4.2 ± 0.6	<0.001	Arababadi et al. ¹⁶
SDF-1 α	48.74 ± 11.35	58.54 ± 9.79	>0.1	Hassanshahi et al. ¹³
Polymorphisms within cytokine and chemokine genes				
IL-10				
C/C	31 (54.4)	22 (22)	<0.001	Arababadi et al. ¹⁶
A/C	24 (42.1)	55 (55)		
A/A	2 (3.5)	23 (23)		
IL-12				
C/C	0 (0)	10 (10)	0.033	Arababadi et al. ¹⁶
A/C	37 (64.9)	54 (54)		
A/A	20 (35.1)	36 (36)		
IFN- γ				
A/A	18 (31.5)	28 (28)	>0.1	Arababadi et al. ¹⁶
A/T	25 (43.8)	47 (47)		
T/T	14 (24.7)	25 (25)		
SDF-1 α				
A/A	6 (10.5)	11 (11)	<0.001	Hassanshahi et al. ¹⁴
A/G	20 (35)	45 (45)		
G/G	31 (28)	44 (44)		
IL-4				
CC	41 (72)	76 (76)	>0.1	Arababadi et al. ¹⁷
CT	13 (23)	22 (22)		
TT	3 (5)	2 (2)		

* Data are reported as mean ± SD or number (%).

TABLE 3. Serum levels of antibodies and complement factors as well as CH50 function in OBI patients and expression levels of CCR5 on the NK cells and T CD8+ lymphocytes

Evaluated factors	OBI patients	Healthy clearance controls	p value	References
Serum levels of antibodies and complement factors (mg/dL)				
IgG	1308.21 ± 68.98	1605 ± 42.29	<0.001	Arababadi et al. ³⁵
IgM	229.8 ± 10.42	160.2 ± 84.53	<0.001	Arababadi et al. ³⁵
IgA	66.96 ± 5.53	63.57 ± 2.11	0.3126	Arababadi et al. ³⁵
C3	76.07 ± 4.691	49.33 ± 2.927	<0.001	Arababadi et al. ³⁵
C4	24.13 ± 1.084	50.71 ± 0.9222	<0.001	Arababadi et al. ³⁵
Complement function (%)				
CH50	183	170	>0.1	Arababadi et al. ³⁵
PBMNCs number status (percentage of total lymphocytes)				
NK cells	11.22 ± 0.2	7.3 ± 0.15	<0.001	Arababadi et al. ⁴⁵
T CD8+ lymphocytes	13.67 ± 0.87	19.60 ± 0.66	<0.001	Arababadi et al. ⁴⁵
Intensity of CCR5				
T CD8+ lymphocytes	5.4 ± 0.45	8.4 ± 0.13	<0.001	Arababadi et al. ⁴⁵
NK cells	1.35 ± 0.10	2.46 ± 0.27	<0.001	Arababadi et al. ⁴⁵

Illustration of the possible interplay between cytokines and the immunologic status in OBI patients

