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Pathogenesis of Dengue

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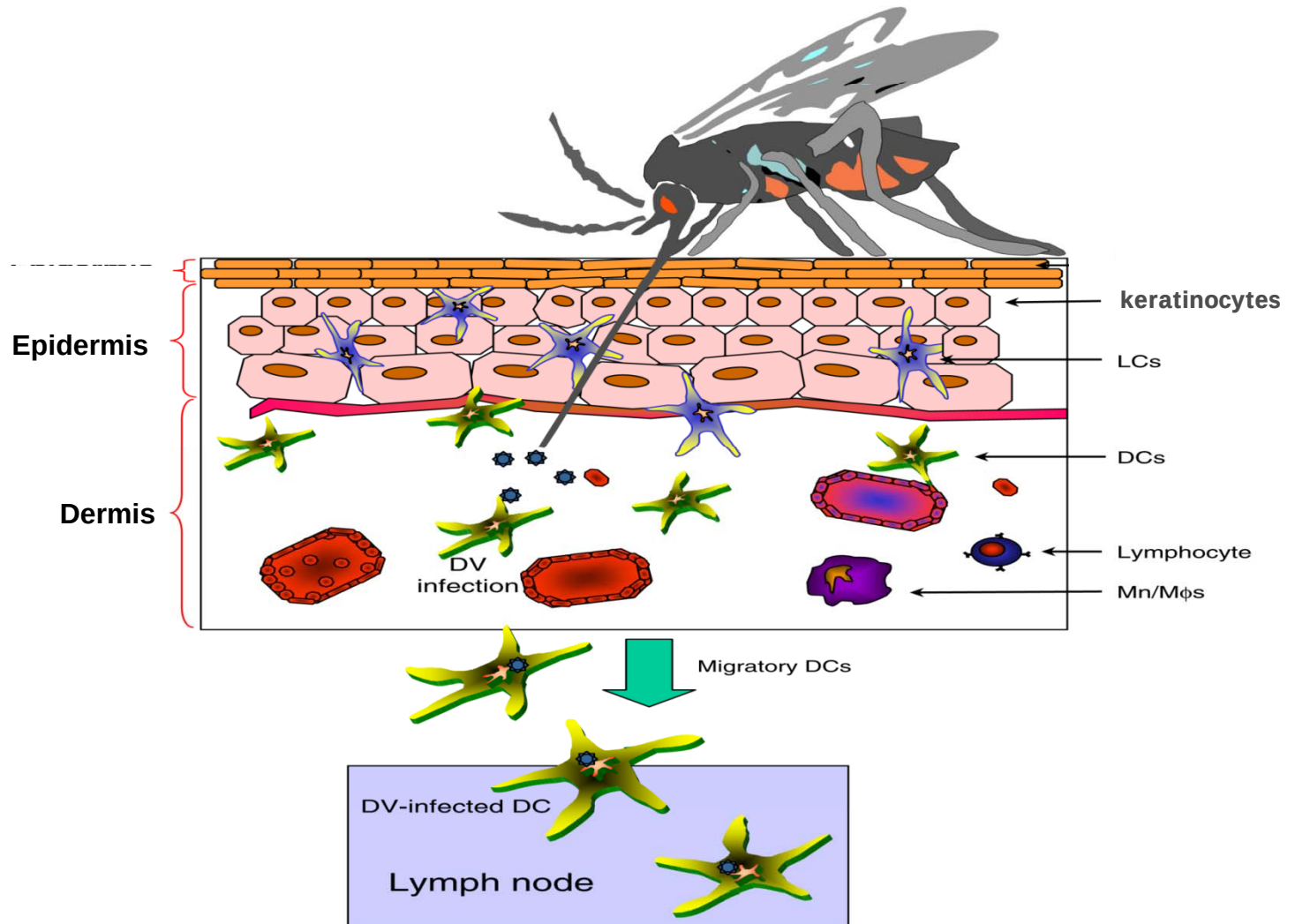
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Infection process

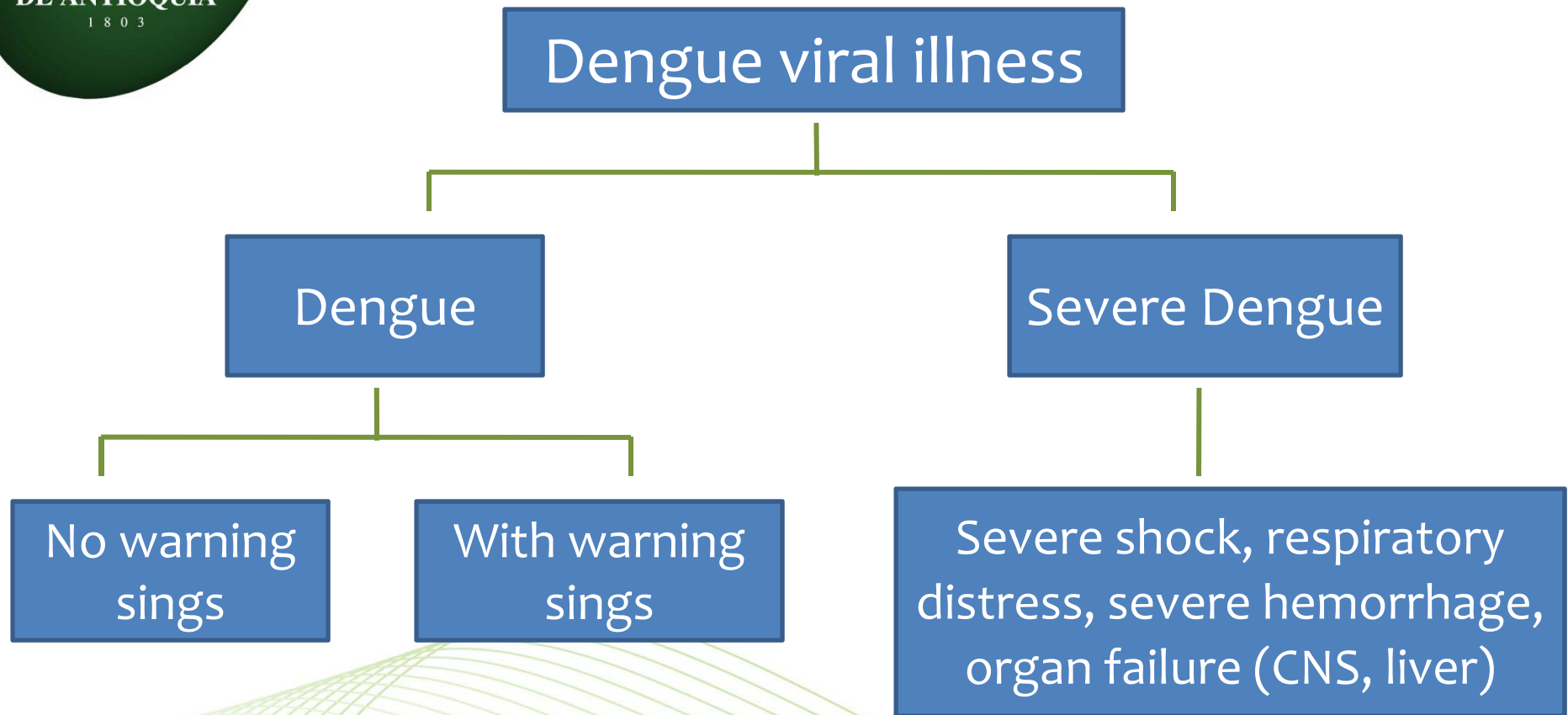
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Clinical forms

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Classification of dengue viral infections, World Health Organization 2009



Pathogenesis of Dengue

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1. Viral factors

2. Genetic factors

3. Immunological factors



1. Viral factors

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- *Tropisms by mononuclear phagocyte lineage.*
- *Low-fidelity replication*
- *Multiple genotypes within each DENV serotype differing in virulence*
- *For example: DENV-2 Southeast Asian genotype is more virulent than the co-circulating DENV-2 American genotype, which almost exclusively caused dengue fever.*



1. Viral factors

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Variations in virulence could be consequence of:

- *DENV tropism (cell susceptibility)*
- *Glycosylation in E and NS1 proteins*
 - *Stabilizing interactions*
 - *Virus particle production*
 - *Binding of the virus particle to DC-SIGN*
 - *Stabilization virus particle*
 - *Efficient secretion of the proteins*



2. Genetic factors

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Evidence:

People of African ancestry do not develop severe dengue





2. Genetic factors

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Polymorphic genes associated to different clinical outcomes

- **FcR γ II**
- *Vitamin D receptor*
- *Glucose 6-phosphate dehydrogenase deficiency*
- *Mannose-binding lectin-2*
- *TNF- α (308A)*
- *CTLA-4*
- *DC-SING*
- *HLA class I and class II alleles: HLA-A*01, HLA-A*24, HLA-A*31, HLA-B*15, HLA-B*46 and HLA-B*51*



3. Immune factors

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Evidence:

Secondary infection with a heterologous serotype or infants born to dengue immune mothers significantly increases the risk of develop severe disease



Secondary dengue virus infection
15-fold to 80-fold risk



3. Immune factors

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Antibody response

Cross-reactive T-cell
response



Cytokine storm

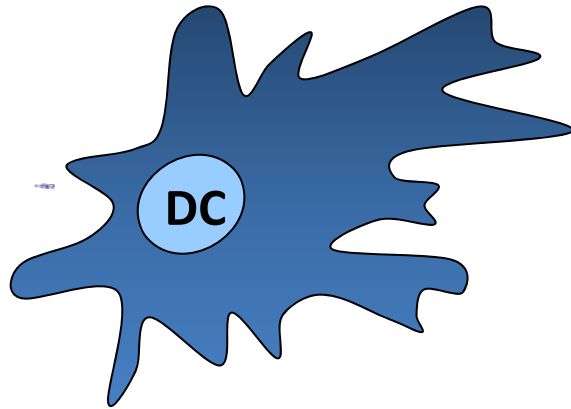
Activation of the
complement system



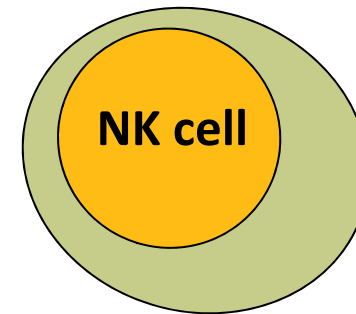
DENV Immune response

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Innate immune response



Cytokines production, antigen presentation and TLR activation



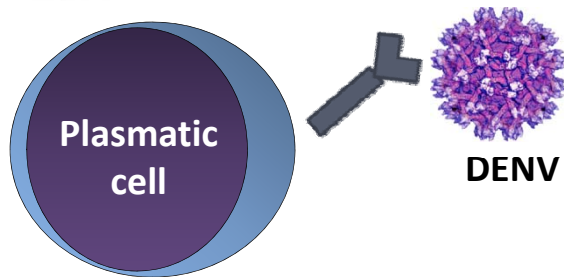
Cytokines production and kill target cells



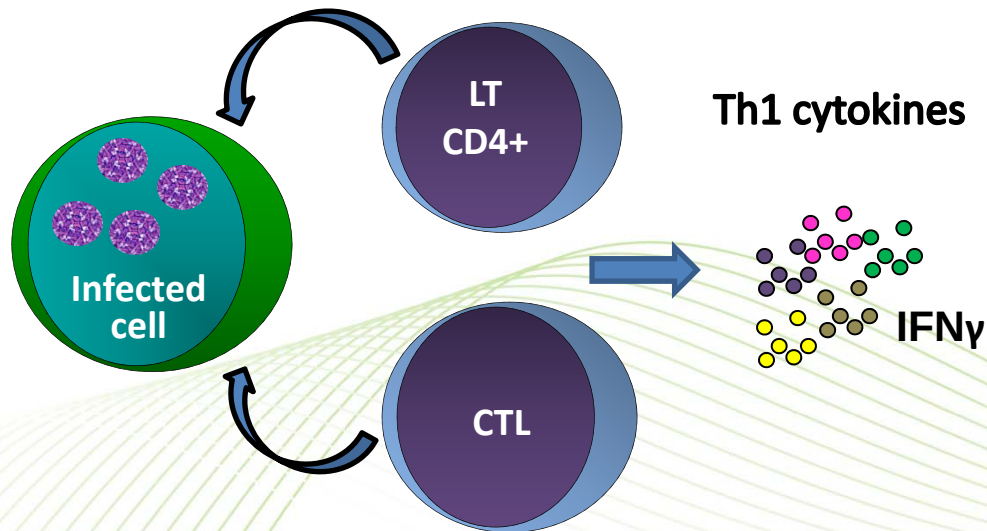
DENV Immune response

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Adaptative immune response



High titres of dengue virus-specific neutralizing antibodies have been associated with a lower risk of severe disease during secondary infection.



Proliferation and target cell lysis

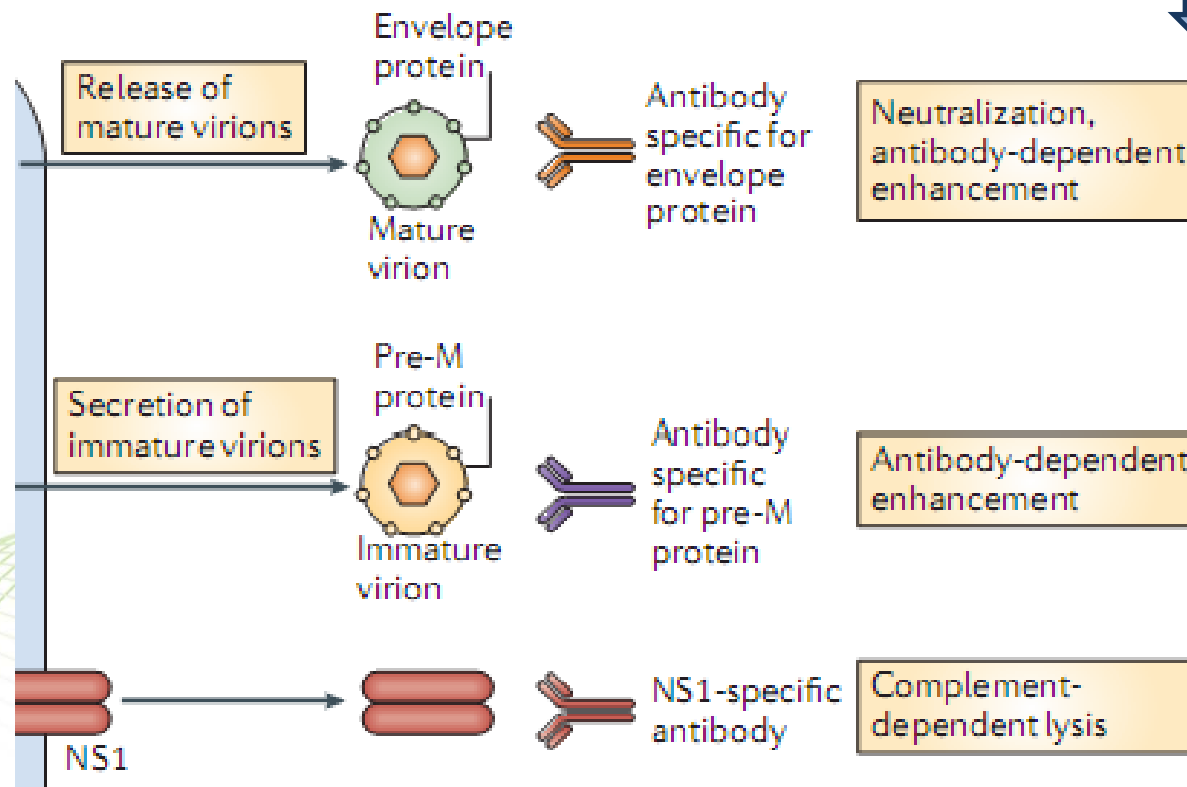


Antibody functions in dengue

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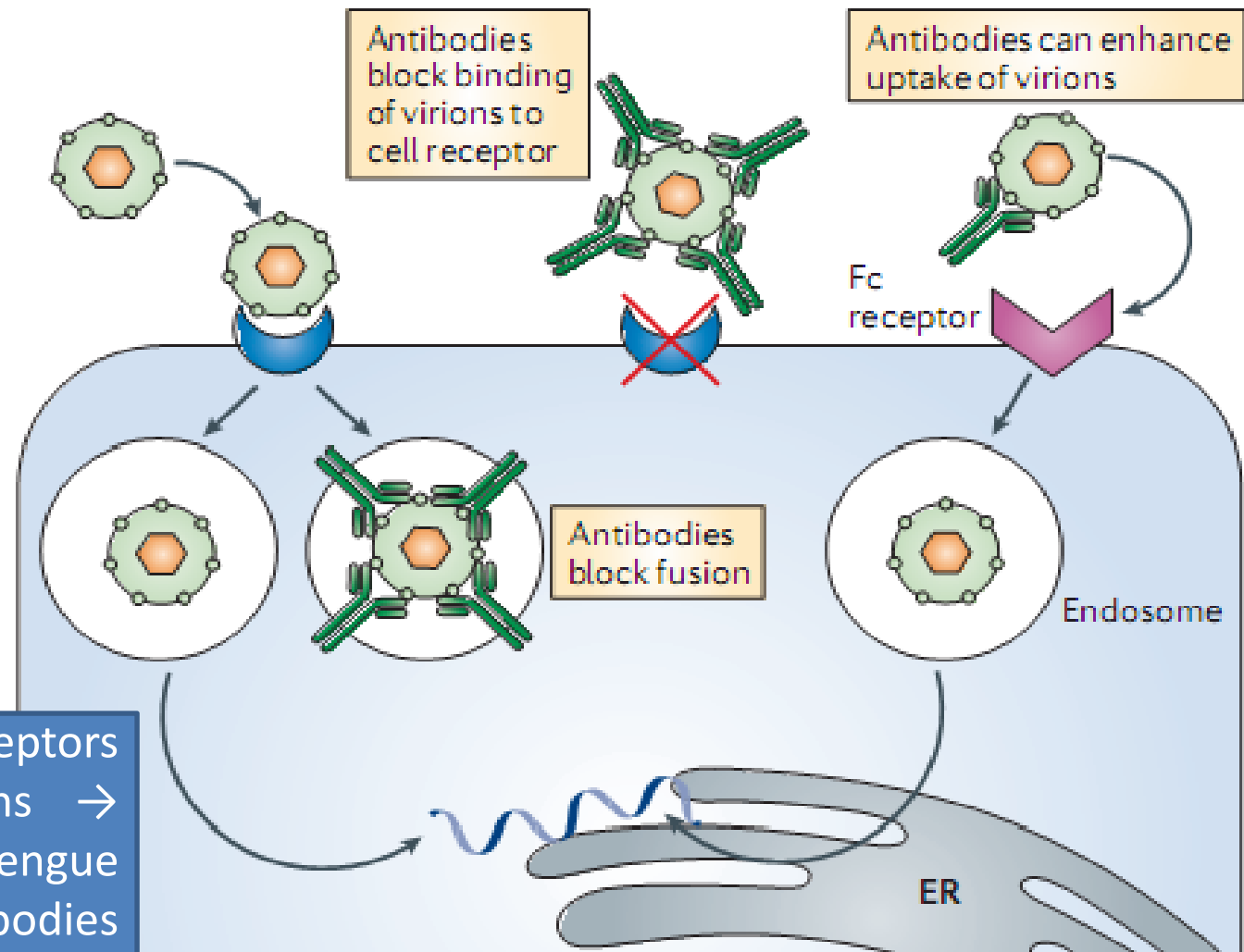
Antibodies can either neutralize or enhance DENV infectivity (dual role)

Sources of antigens



Antibody dependent enhancement

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Cells expressing receptors for immunoglobulins → opportunity for dengue virus-specific antibodies to enhance viral entry



Autoimmunity

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Antibody response

E protein- specific
antibodies

Plasminogen

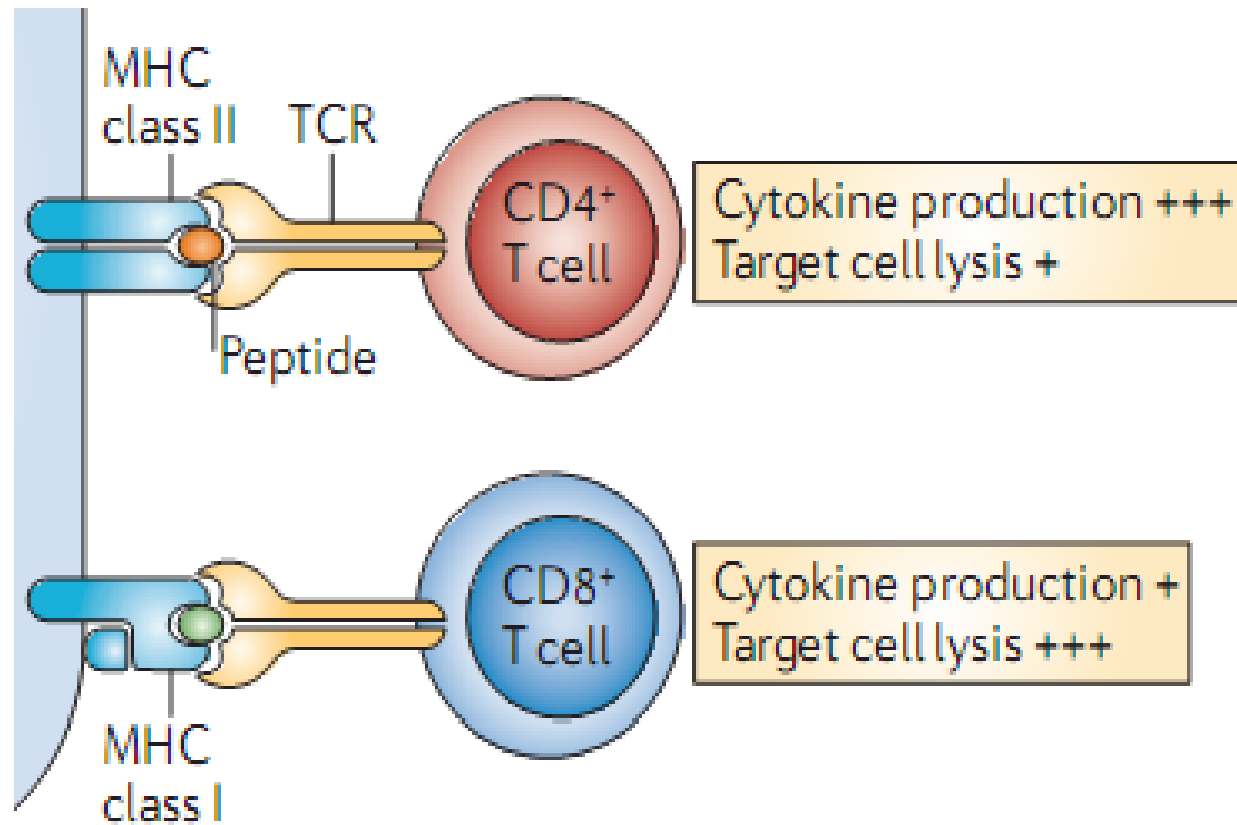
NS1 protein- specific
antibodies

Proteins of
coagulation and
endothelial cell-
expressed proteins

Activation of coagulation pathways
and alteration in endothelial cell function

Cross-reactive T-cell response and cytokines

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Reactivity to more than one
dengue virus serotype



Induction or enhancement of inflammation
and the alteration of vascular permeability.



Activation of the complement system

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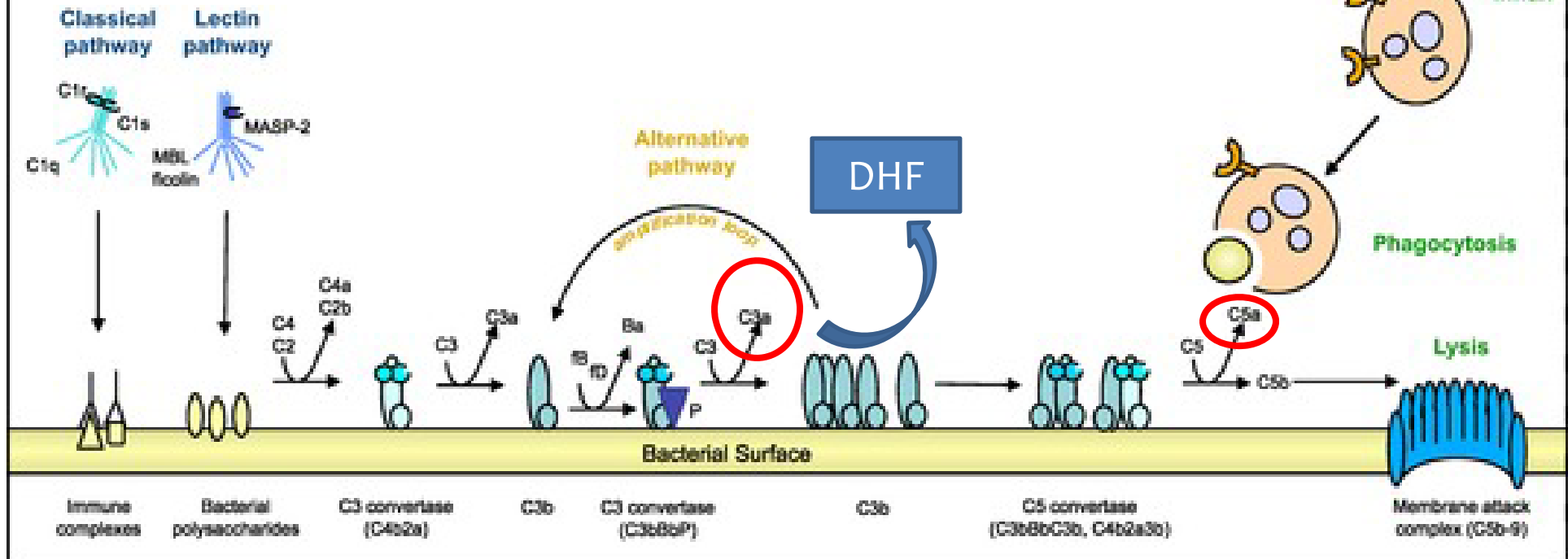
J Mol Med 88 (2010) 115–120

Recognition & Activation

Amplification & Opsonization

Effector functions

DENV-antibodies
immune complex





Plasma markers associated with outcome

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Cytokines

TNF, IFN γ , IL-6, IL-8, others

Soluble receptors

TNF receptor and IL-2 receptor

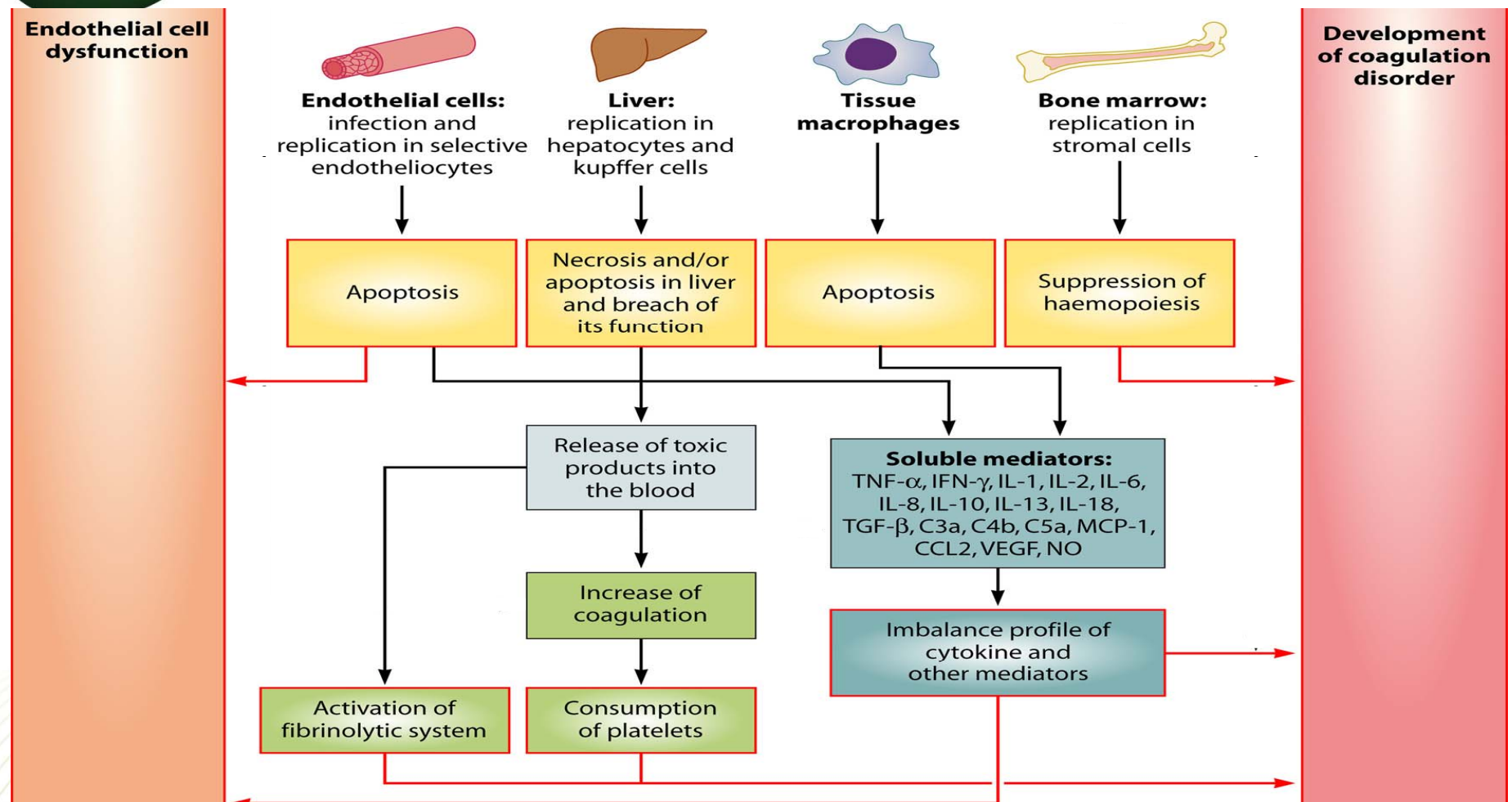
Coagulation factors or endothelial cell markers

Von Willebrand factor, tissue factor, plasminogen activator inhibitor,

Damage to specific tissues

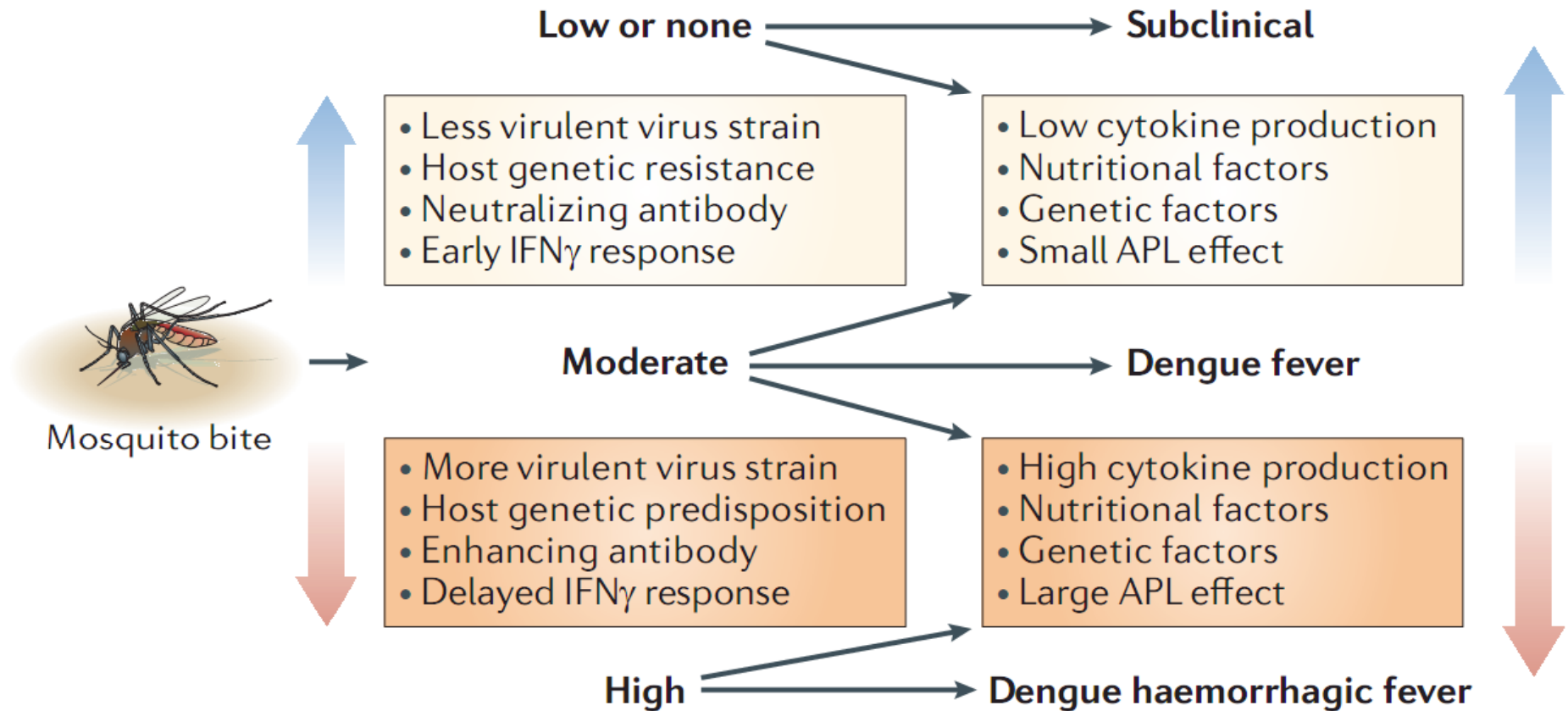
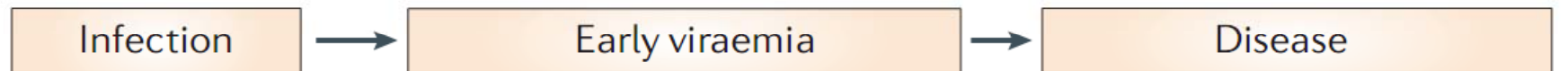
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Clin. Microbiol. Rev. 2009, 564–581



In summary...

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Research targets

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- *Mechanisms by which innate immunity regulates memory B- and T-cell generation, maintenance, and activation during primary and secondary DENV infections*
- *Role of autoimmunity in dengue pathogenesis*
- *Role of DENV immune complexes in the signaling network within target cells, especially APCs, and how it influences virus replication and priming of immune responses*

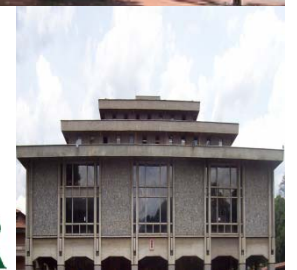


Research targets

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- *Identifying soluble factors inducing endothelial cell dysfunction and coagulopathy seen in DHF/DSS*
- *Identifying critical components of tight junctions and adherent junctions present in the vascular beds affected during DHF/DSS*
- *Understanding race- and age-dependent susceptibility to severe DENV infection*

Muchas gracias !



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