Imunodeficiente primare

(IDP)

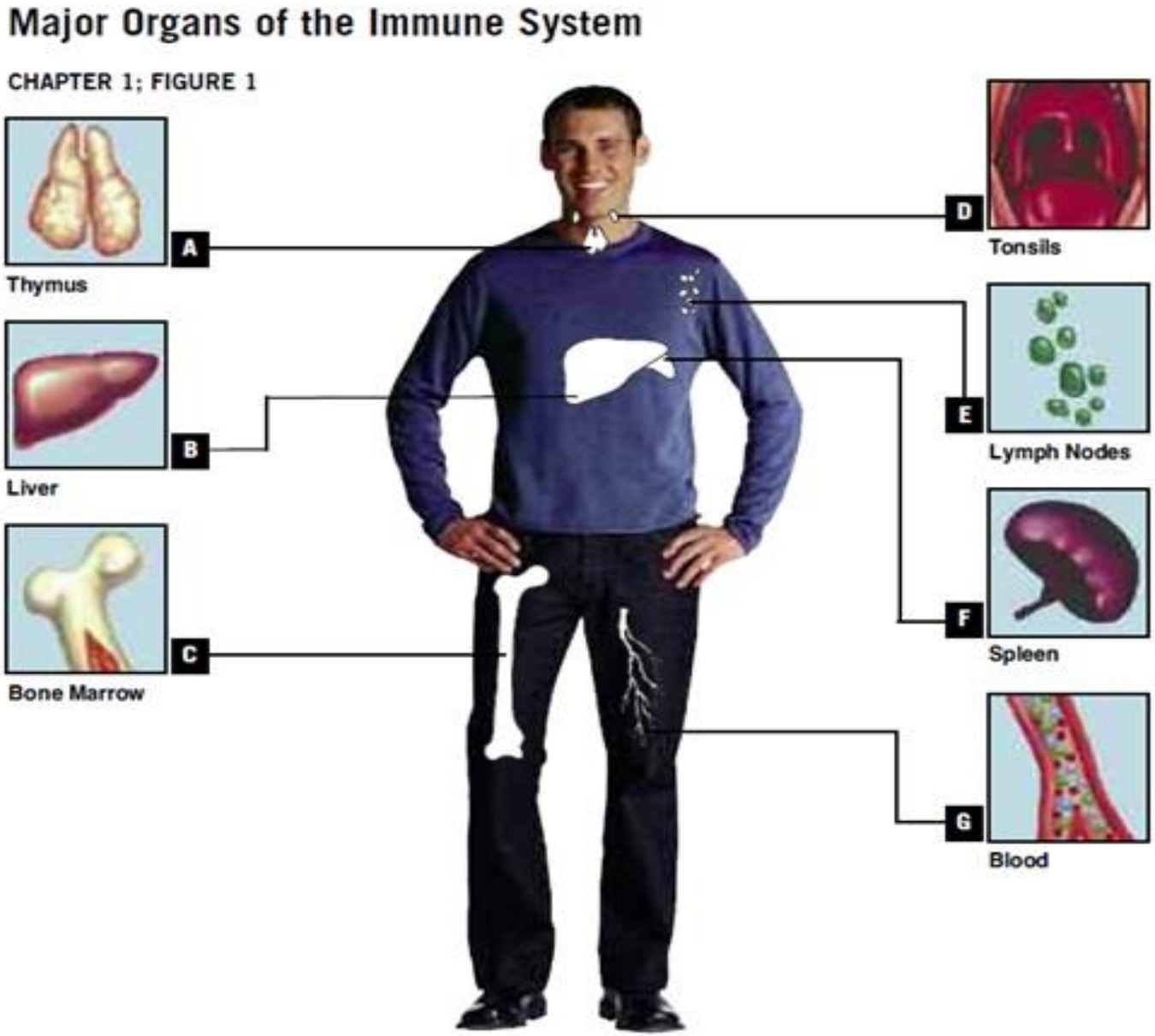
Care este rolul sistemului imun ?

- **De a distinge selful de nonself**

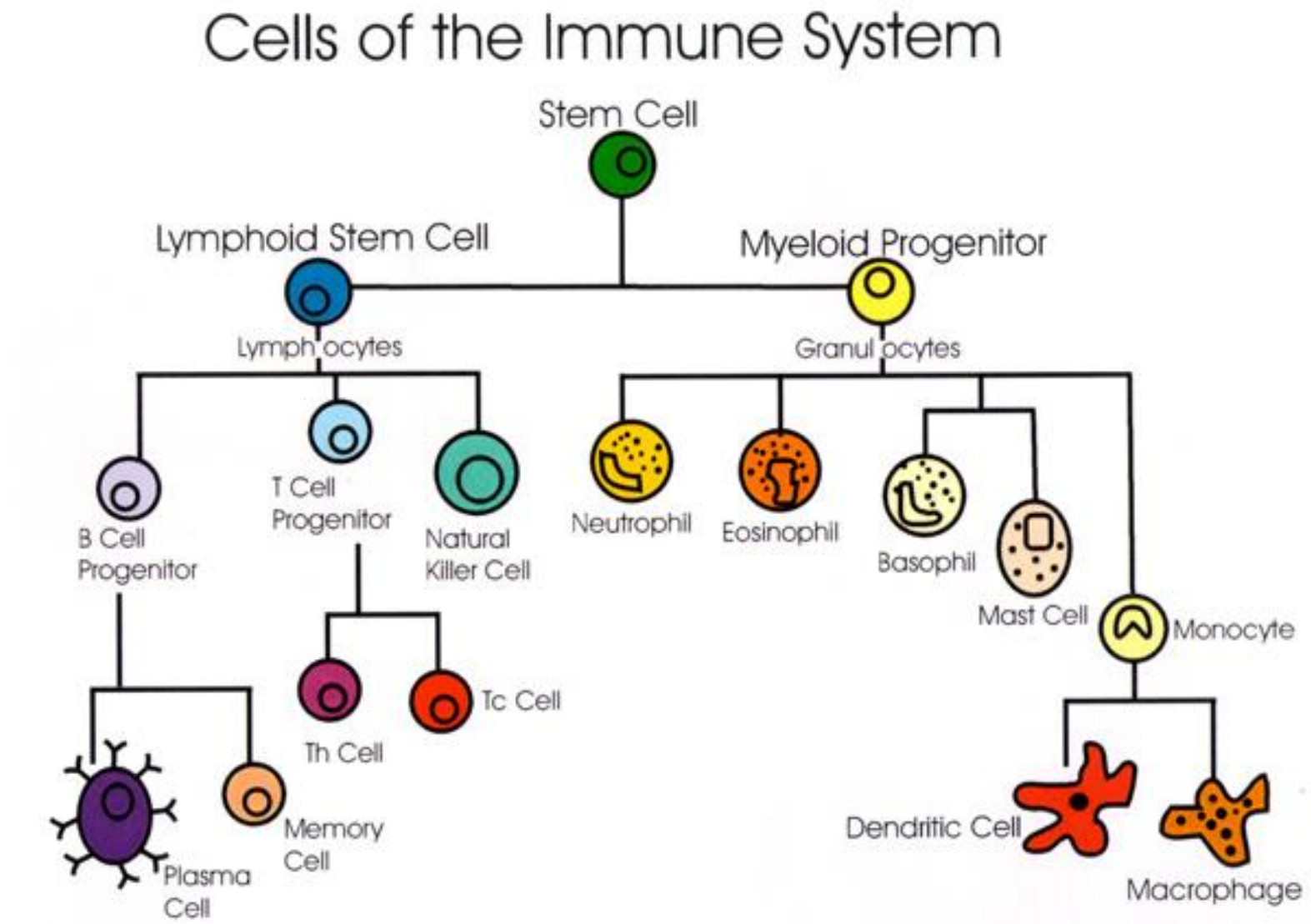
- **prezervarea antigenelor proprii**
- **recunoasterea substantelor si agentilor straini si**
- **eliminarea sau neutralizarea sau metabolizarea lor**

- **De a proteja organismul de infectii, boli autoimune si de malignitati**

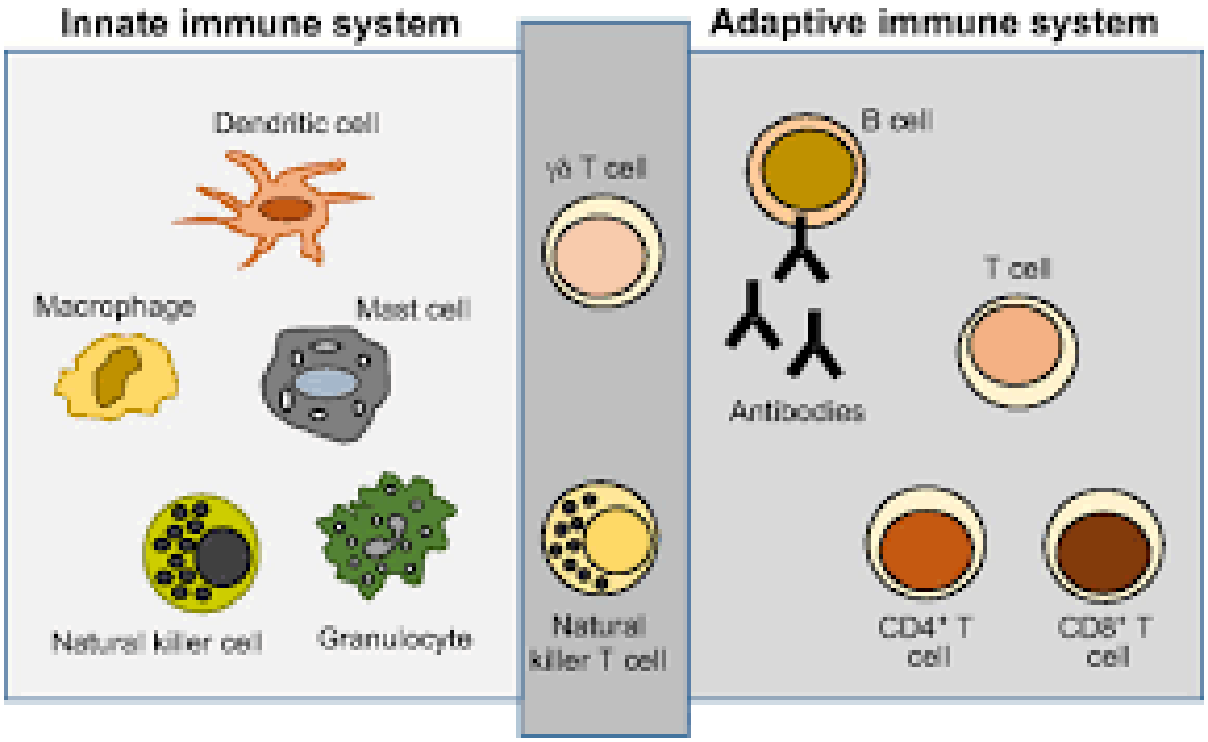
Care sunt organele sistemului imun?



Care sunt celulele sistemului imun?



Care sunt compartimentele sistemului imun?



Innascut
Nespecific

Adaptativ
Specific

Imunitatea specifica

Umorala

Apararea extracelulara

impotriva

bacteriilor si virusurilor

Celulara

- **Apararea intracelulara**

impotriva

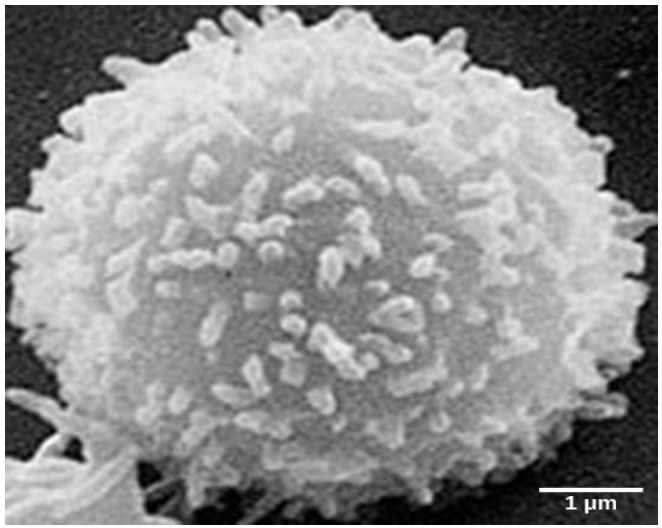
virusurilor, fungilor, parazitilor

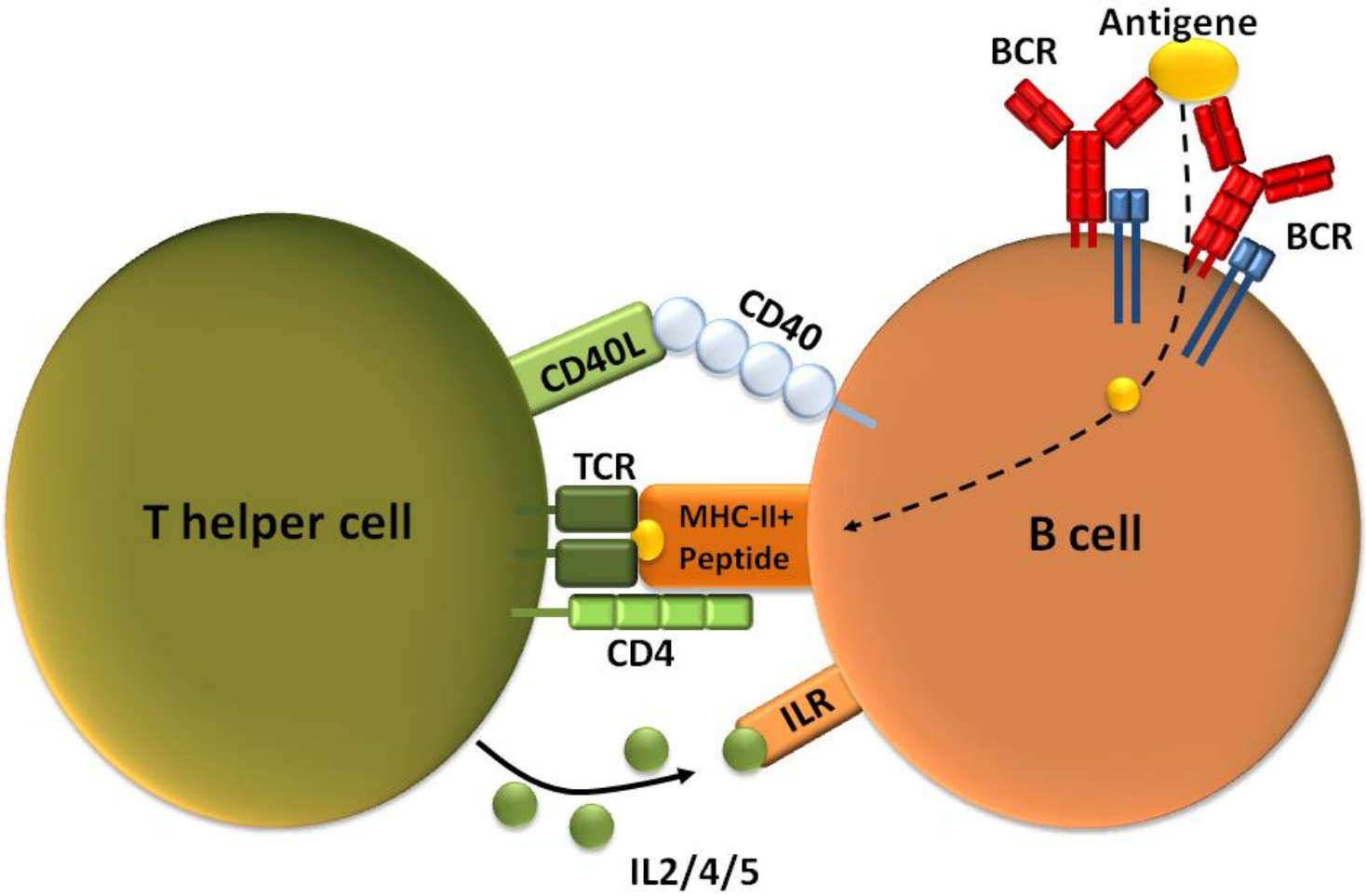
- **supravegherea imuna impotriva celulelor maligne corpurilor straine (transplant)**

Producerea de anticorpi

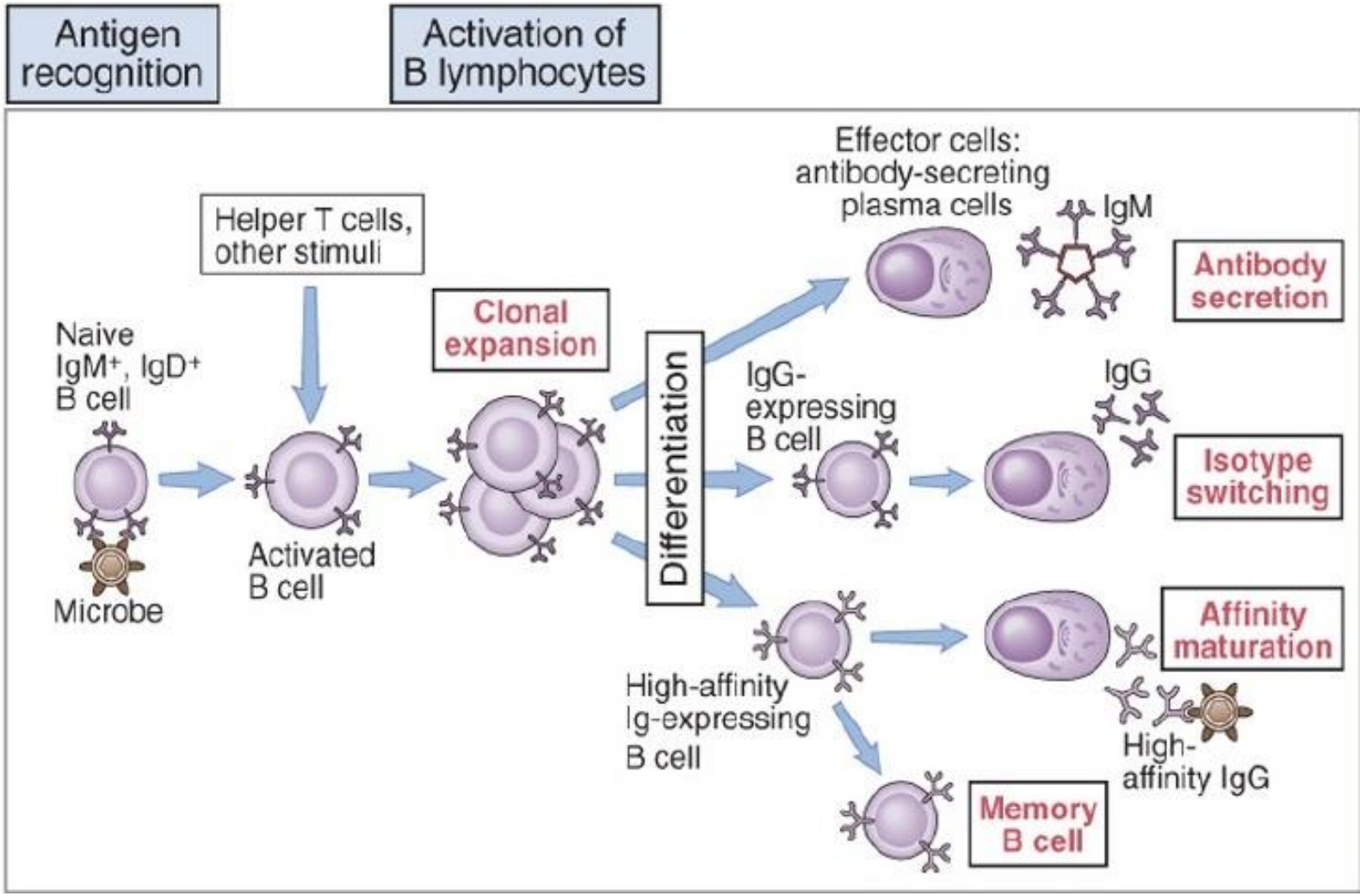
Principalul actor

Limfocitul B

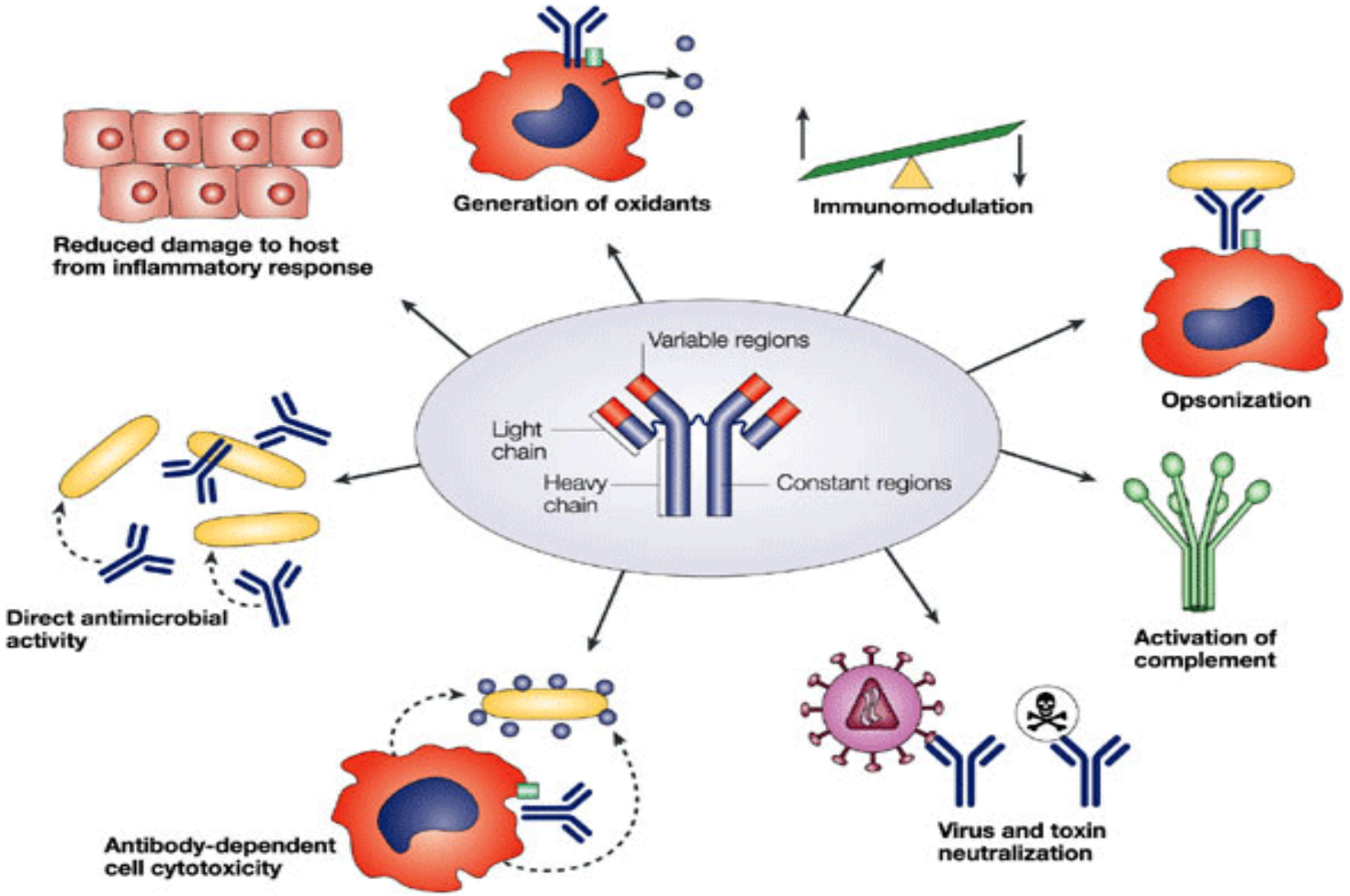


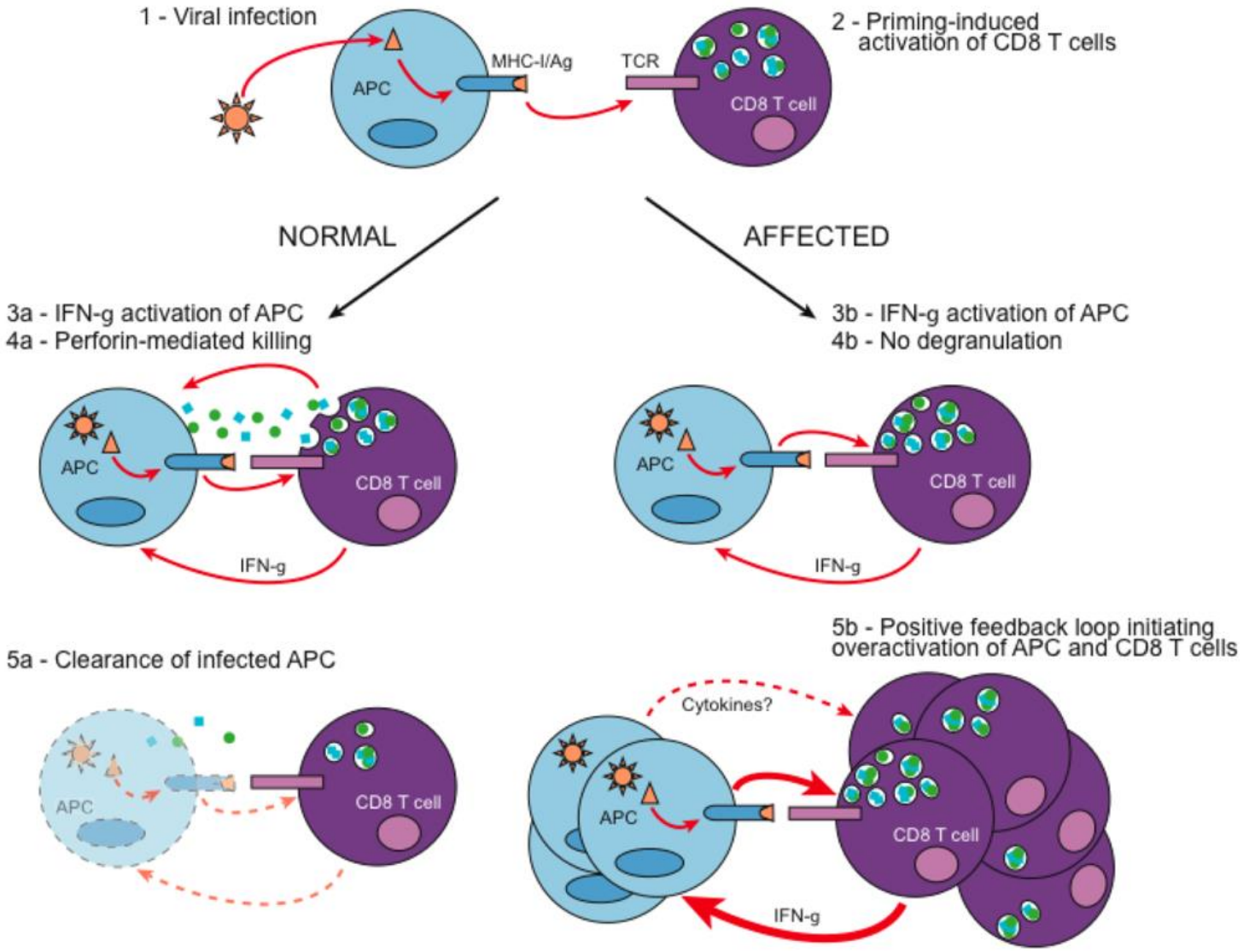

Antigene
BCR
BCR
CD40L
CD40
TCR
T helper cell
MHC-II+
Peptide
B cell
CD4
ILR
IL2/4/5

Sinteza anticorpilor



Modul de acţiune al anticorpilor




1 - Viral infection
APC
MHC-I/Ag
TCR
CD8 T cell
2 - Priming-induced activation of CD8 T cells
NORMAL
AFFECTED
3a - IFN-g activation of APC
4a - Perforin-mediated killing
APC
CD8 T cell
IFN-g
3b - IFN-g activation of APC
4b - No degranulation
APC
CD8 T cell
IFN-g
5a - Clearance of infected APC
APC
CD8 T cell
5b - Positive feedback loop initiating overactivation of APC and CD8 T cells
Cytokines?
APC
CD8 T cell
IFN-g

IDP

Definitie

-susceptibilitate patologica la infectii,

-boli autoimune sau autoinflamatorii

-incidenta mare a malignitatilor

Nediagnosticate
Diagnosticate greşit
Diagnosticate tardiv

Complicaţii frecvente → infecţiile
Leziuni ireversibile
Deces precoce

IDP

Epidemiologie

- **Boli rare : Incidenta: ~ 1:2000 (1:250)**

Cel mai frecvent: deficitul de IgA : 1: 310-2170 persoane

Cel mai frecvent diagnosticat= CVID (Imunodeficienta comuna variabila)

IDP
Clasificare

> 400 de tipuri

Exista mai multe clasificari:

- **In functie de defectul molecular**
- **In functie de celula defectuoasa**

IDP

Clasificare

I. IDP ale celulelor B

II. IDP ale celulelor T si combinate B si T

III. IDP ale fagocitelor

IV. ID ale sistemului complement

Imunodeficienţe Primare

Primul pas: să ne gândim la IDP

INFECŢII

AUTOIMUNITATE / AUTOINFLAMAŢIE

CANCER

Istoric familial pozitiv

FALIMENTUL CREŞTERII

Când ne gândim la o IDP?

Susceptibilitate patologică la INFECȚII

Intensitate
Evoluţie
Număr
Localizare
Tip de agent patogen

Imunodeficienţe Primare

INFECŢII

- **Severe**

- **Persistente**

- virale > 7 zile

- bacteriene > 21 zile

- **Recurente**

La vârsta preşcolară sunt acceptate până la 12 infecţii/an

-3-8 infectii de tract respirator superior şi

- până la 5 episoade de gastroenterocolită / an

Susceptibilitate patologică la infecţii

Localizare

- **Profunde:** **(Bronho) pneumonii,**
  Sinuzite
  Abcese de organ recurente neexplicate
  Diaree trenantă

- **Sistemice:** **Septicemie**
  Meningită
  Osteomielită

- **Politope**

Imunodeficienţe Primare

INFECŢII

- **Cu germeni oportunişti**

Susceptibilitate patologică la infecţii

- **Agent patogen**

Bacterii

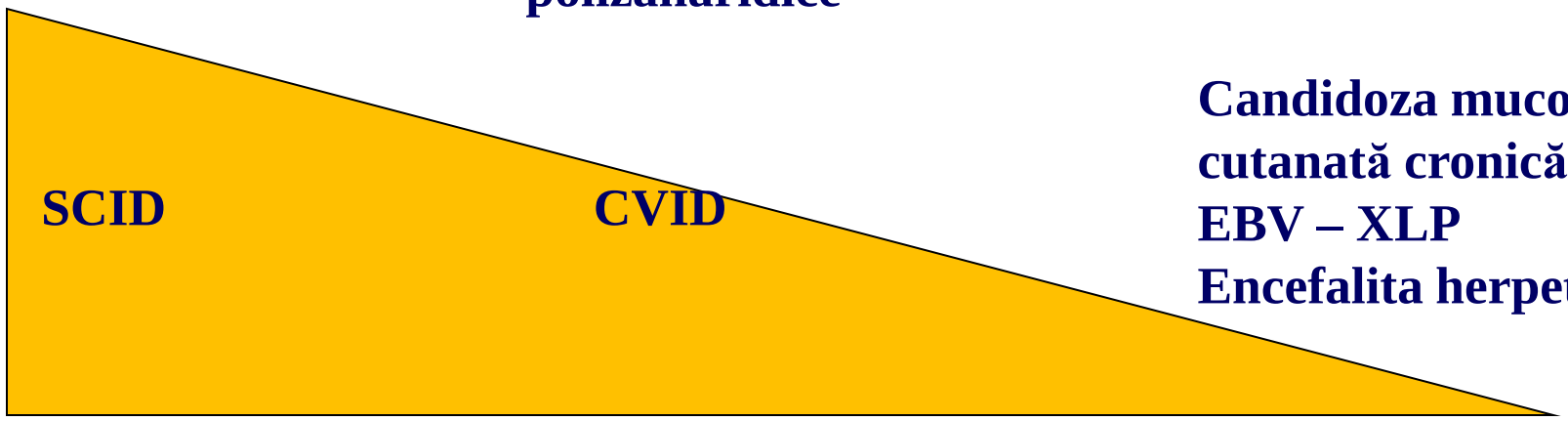
Virusuri

Fungi

Oportunişti

Antigene polizaharidice

Un singur patogen



Imunodeficienţe Primare

INFECŢII

- **Reacţii postvaccinale severe (BCG-ită, polio)**
- **Istoric familial de deces la vârstă mică prin infecţie**

Cand trebuie sa suspectam o ID?

2. Boli imune sau autoimune

- Trombocitopenie
- Anemie hemolitica
- Anemie aplastica
- Colagenoze
- Artrita reumatoida juvenila
- Diabet zaharat
- Tiroidita
- Altele

Cand trebuie sa suspectam o ID?

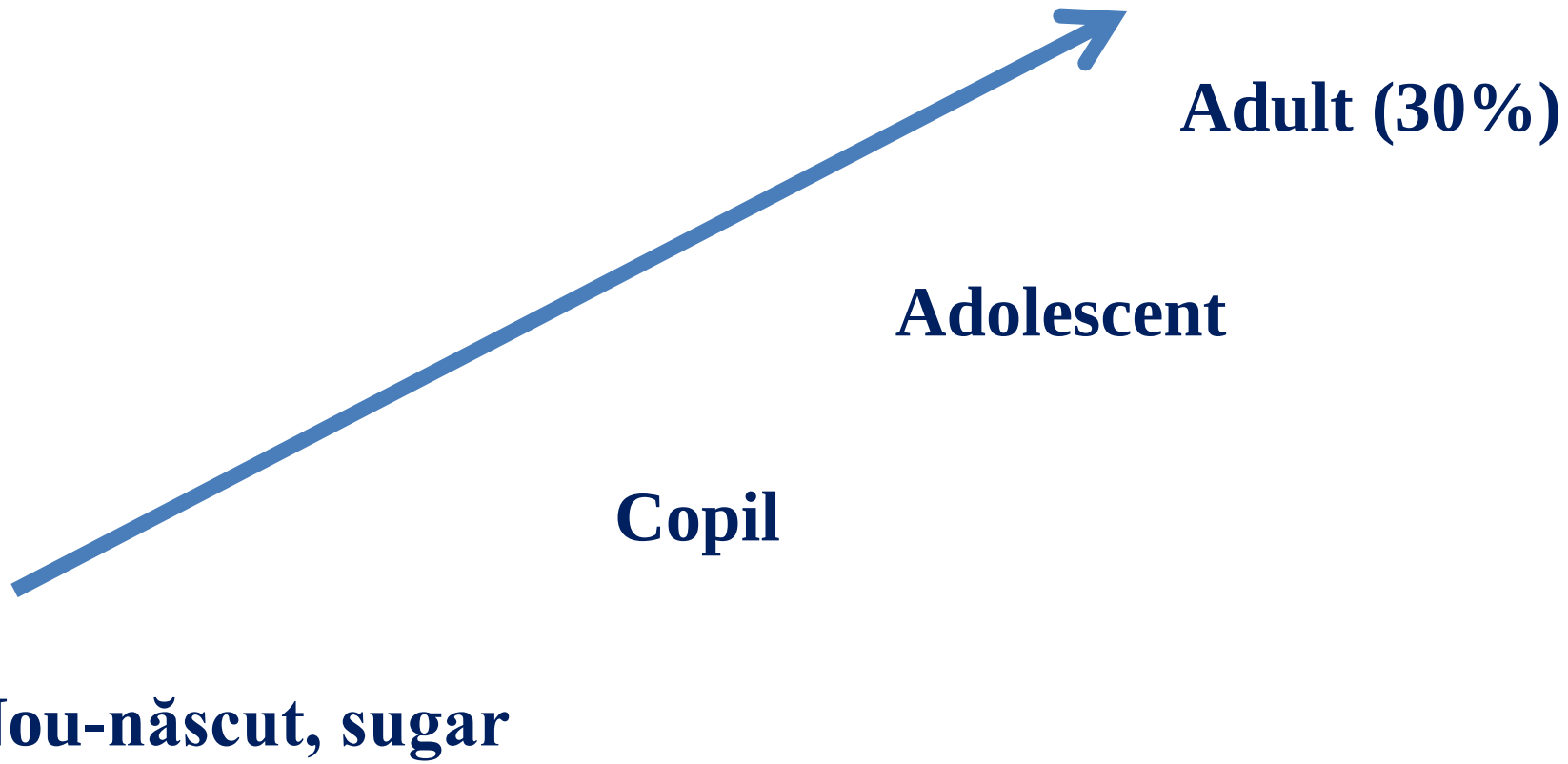
3. Boli pulmonare obstructive cronice (bronsiectazii)

4. Cancer

5. Absenta timusului (Rx) sau a organelor limfatice (ganglioni, si amigdale)

6. Falimentul cresterii

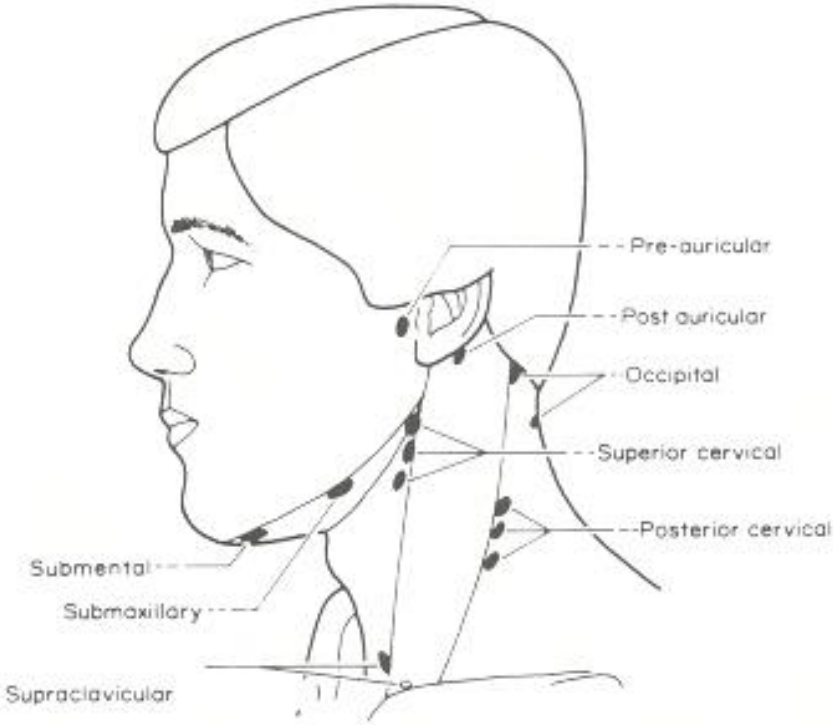
Vârsta de debut



Examen clinic

Falimentul creşterii

Absenţa ganglionilor şi a amigdalelor

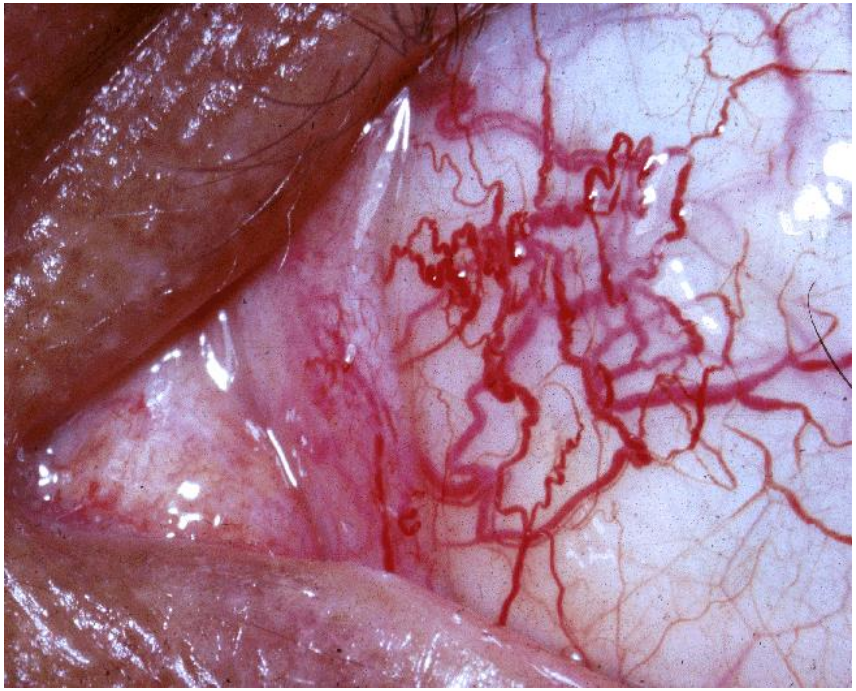


Normal Healthy Throat and Airway.

Enlarged Crowded Tonsils.

Ulceraţiile mucoasei bucale

Leziunile conjunctivale de tip telangiectatic



IDP

Explorari

1. **Nespecifice**

- Hemograma

Numar (valoarea absoluta)

- neutrofile,
- limfocite,

- trombocite

Definiţie

NEUTROPENIA

Neutrofile < 1000/mmc în primul an de viaţă

Neutrofile < 1500/mmc după primul an de viaţă

Definitie

LIMFOPENIA

Limfocite < 3000/mmc <3 ani

Limfocite < 1500/mmc > 3 ani

Limfocite < 1000/mmc la adult

2) Specifice

- **γ globuline (Elfo proteine)**
- **imunograma: IgA, IgG, IgM**
- Subclase de IgG (IgG1, IgG2, IgG3, IgG4)
- Raspunsul la vaccinare (anticorpi antidifterici, antitetanici, antipneumococici)

IDP
Explorari

2) Specifice

- **Subpopulatii limfocitare (LfB, LfT, CD4+, CD8+, NK)**
- Teste de proliferare limfocitara
- Componentele complementului
- Test de fagocitoza, **NBT, burst**

- Rx timus - ± absent

Rx normala la sugar – prezenta timusului

- **Identificarea agentului patogen cauzator de infectie este obligatorie**

- Ne va orienta spre tipul de IDP
- Ne va permite un tratament corect

IDP
Diagnostic diferential

- Statusul post infectii virale
- Infectia HIV (excludere prin PCR)

- Boli metabolice

- Malabsorbtia cu pierdere de proteine
- Sindromul nefrotic

- Agentii imunosupresivi

IDP
Diagnostic diferential

- Splenectomie

- Boli maligne

- Expunere crescuta la infectii (intrarea in colectivitate – gradinita, scoala)

IDP
Diagnostic diferential

In cazul infectiilor respiratorii recurente:

- Boala cililor imotili
- Mucoviscidoza
- Boala alergica
- Refluxul gastroesofagian
- Fistula esofagobronsica
- Corpul strain

Imunodeficienţe primare

Predominant umorale	Combinate T şi B	ID fagocitului	Ale sistemului complement
Deficitul de IgA **Boala Bruton** **CVID** **(ID comună variabilă)**	**SCID** **(ID combinată severă)**	**Neutropeniile congenitale** **Boala granulomatoasă cronică (septică)**	**Angioedemul recurent**

IDP
Tratament

Masuri generale

-Se contraindica vaccinarea cu virusuri vii

(IDP celulare T)

-Toate produsele de sange trebuie iradiate pentru a preveni reactia grefa contra gazda

IDP
Tratament

Tratament specific :

- substitutia cu Ig (IV sau subcutanat)

- citokine
- IFN-γ in boala granulomatoasa cronica
- G-CSF – neutropenia severa

IDP
Tratament

Transplantul medular – in toate IDP celulare T si cele in care este alterata functia celulei implicate

Terapie genica

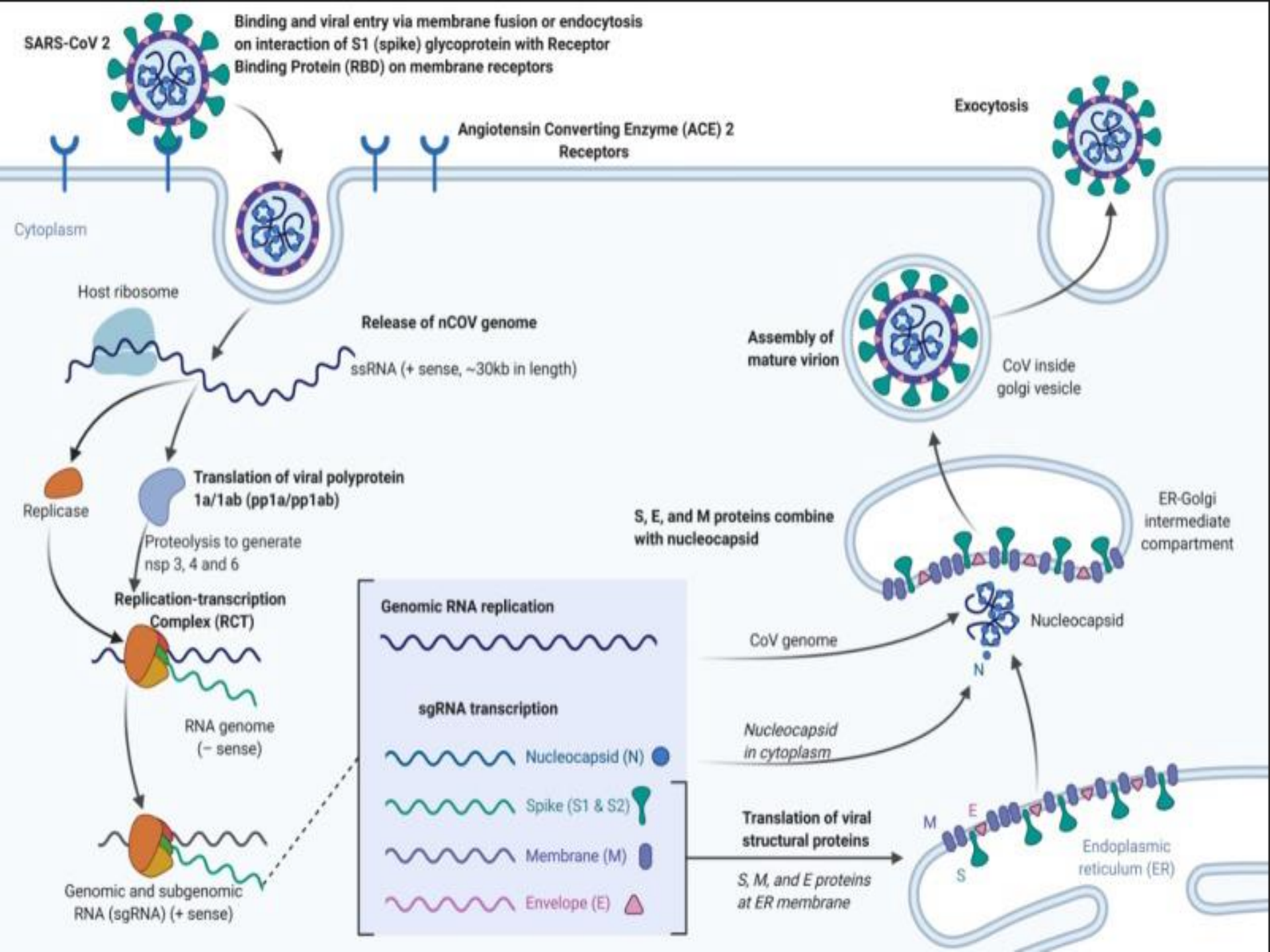
IDP
Prognostic

In general ameliorat

Ramane infaust in IDP T si SCID

Este mai bun in defectele celulare B


GETTY IMAGES


SARS-CoV 2
Binding and viral entry via membrane fusion or endocytosis on interaction of S1 (spike) glycoprotein with Receptor Binding Protein (RBD) on membrane receptors
Angiotensin Converting Enzyme (ACE) 2 Receptors
Exocytosis
Cytoplasm
Host ribosome
Release of nCOV genome
ssRNA (+ sense, ~30kb in length)
Assembly of mature virion
CoV inside golgi vesicle
Replicase
Translation of viral polyprotein 1a/1ab (pp1a/pp1ab)
Proteolysis to generate nsp 3, 4 and 6
S, E, and M proteins combine with nucleocapsid
ER-Golgi intermediate compartment
Replication-transcription Complex (RCT)
Genomic RNA replication
CoV genome
Nucleocapsid
N
RNA genome (– sense)
sgRNA transcription
Nucleocapsid in cytoplasm
Nucleocapsid (N)
Spike (S1 & S2)
Membrane (M)
Envelope (E)
Translation of viral structural proteins
S, M, and E proteins at ER membrane
M
E
S
Endoplasmic reticulum (ER)
Genomic and subgenomic RNA (sgRNA) (+ sense)

Features, Evaluation and Treatment Coronavirus (COVID-19)

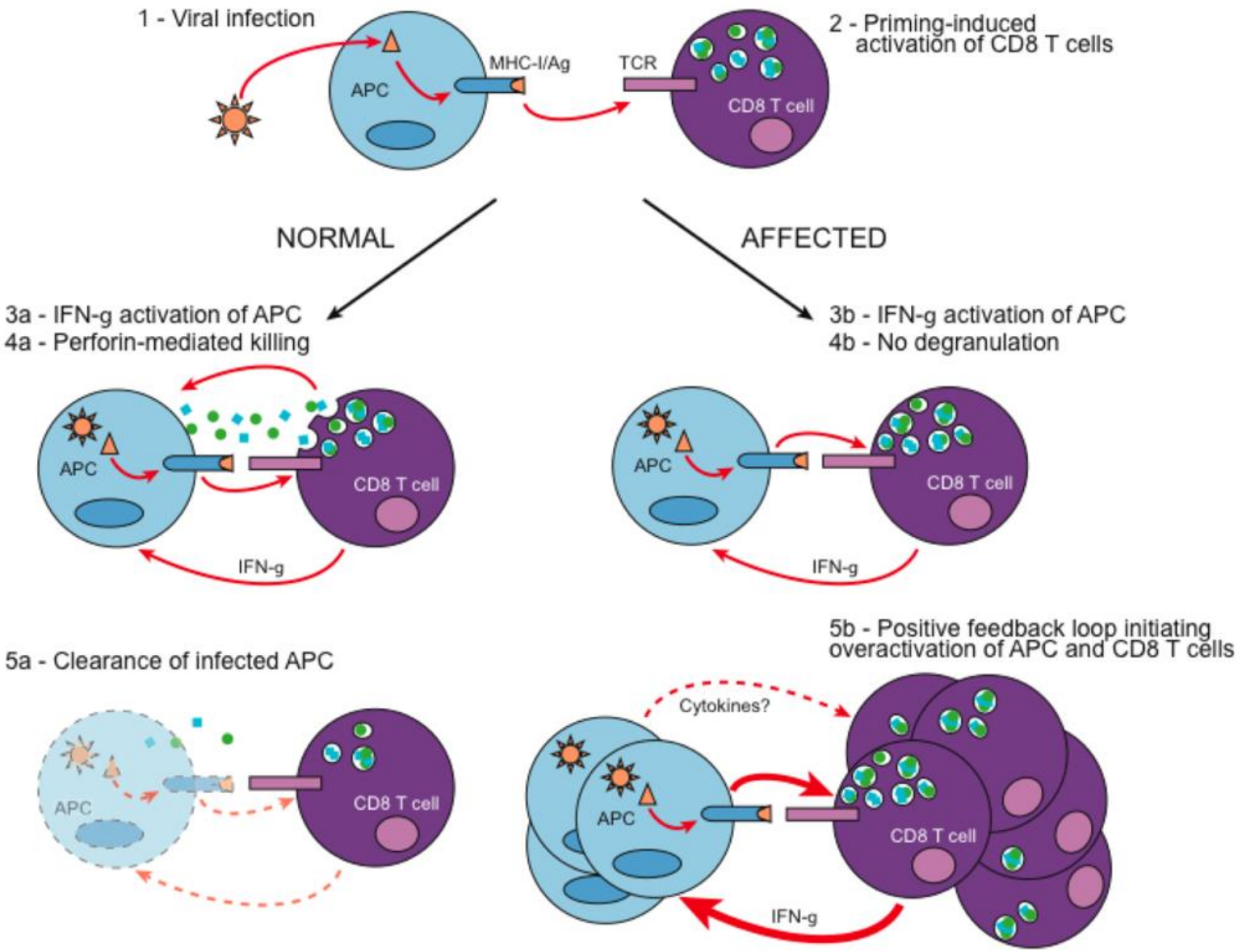
Marco Cascella; Michael Rajnik; Arturo Cuomo; Scott C. Dulebohn; Raffaela Di Napoli.

links to the function of the nsps and structural proteins. For instance, research underlined that nsp is able to block the host innate immune response.[7] Among functions of structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release. However, many of these features (e.g., those of nsp 2, and 11) have not yet been described.

subunits (S1 and S2). Homotrimers of S proteins compose the spikes on the viral surface, guiding the link to host receptors.[8] Of note, in SARS-CoV-2, the S2 subunit — containing a

capable of producing an excessive immune reaction in the host. In some cases, a reaction takes place which as a whole is labeled a 'cytokine storm'. The effect is extensive tissue damage. The protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells, and inhibits the growth of others. It also stimulates the production of acute phase proteins and plays an important role in thermoregulation, in bone maintenance and in the functionality of the central nervous system. Although the main role played by IL-6 is pro-inflammatory, it can also have anti-inflammatory effects. In turn, IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases and some types of cancer. It is also implicated into the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction.

Concerning laboratory examinations, in the early stage of the disease, a normal or decreased total white blood cell count and a decreased lymphocyte count can be demonstrated. Lymphopenia appears to be a negative prognostic factor. Increased values of liver enzymes, LDH, muscle enzymes, and C-reactive protein can be found. There is a normal procalcitonin value. In critical patients, D-dimer value is increased, blood lymphocytes decreased persistently, and laboratory alterations of multiorgan imbalance (high amylase, coagulation disorders, etc.) are found.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3a - IFN-g activation of APC
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5a - Clearance of infected APC
APC
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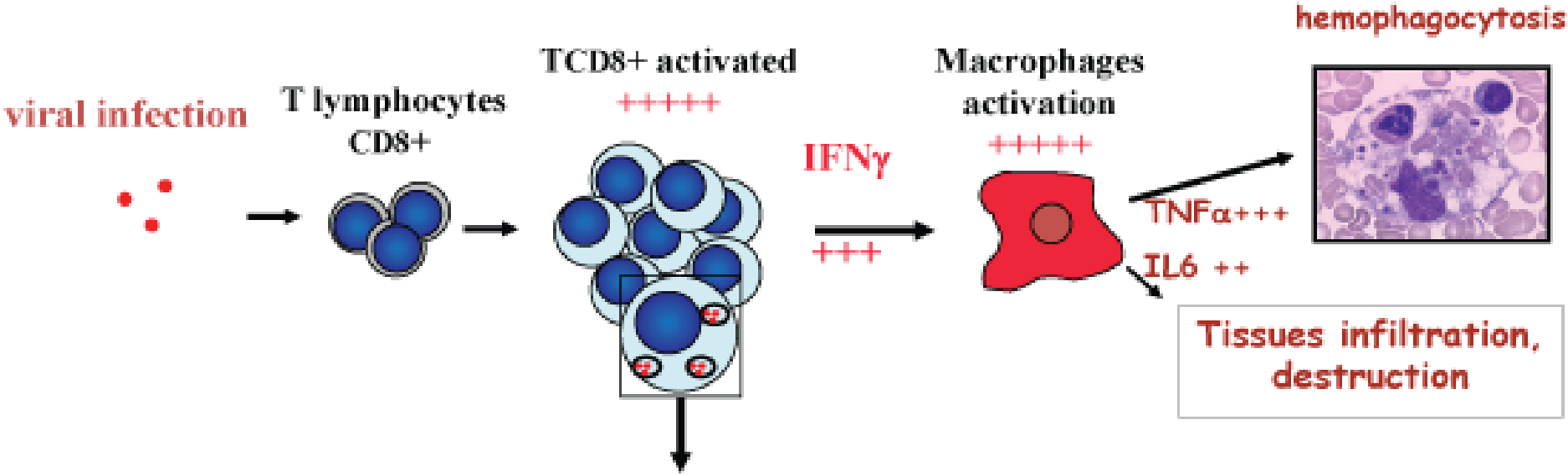
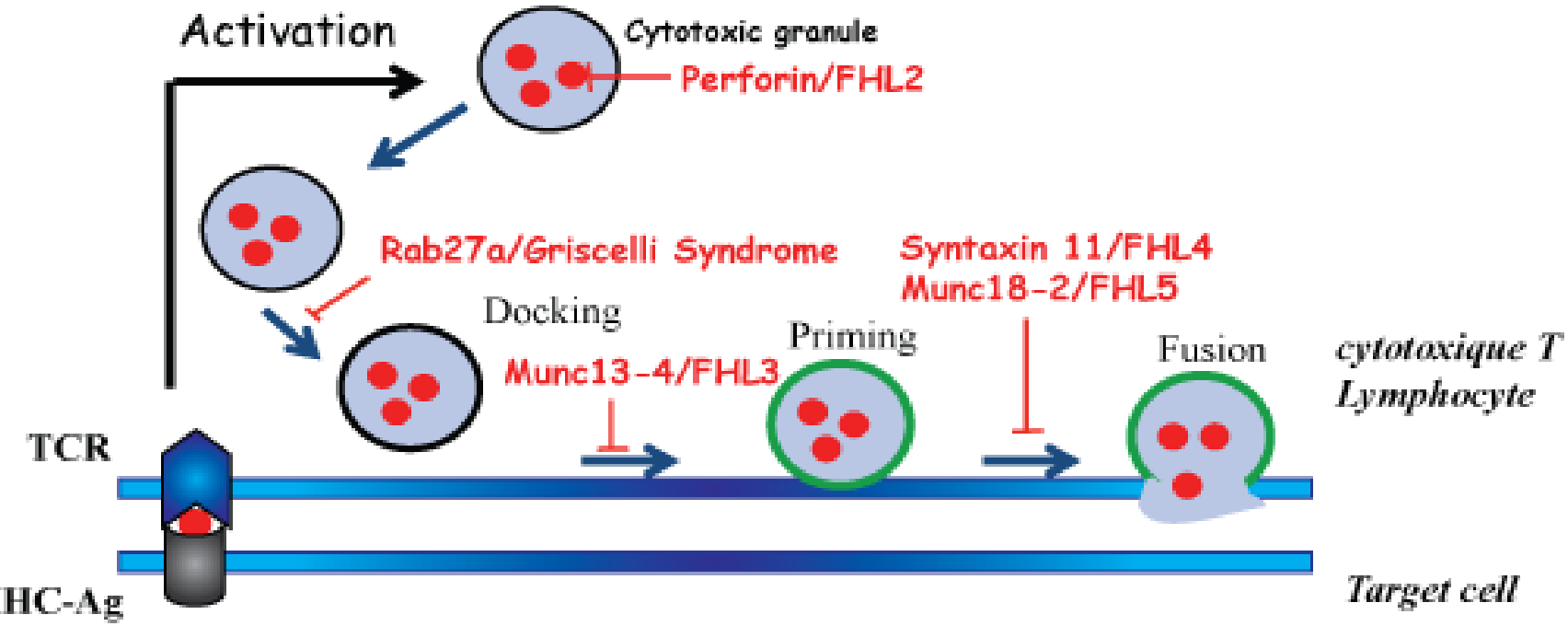
5b - Positive feedback loop initiating overactivation of APC and CD8 T cells
Cytokines?
APC
CD8 T cell
IFN-g

Hemophagocytic lymphohistiocytosis (HLH)





Treatment of refractory hemophagocytic lymphohistiocytosis with emapalumab despite severe concurrent infections