# Psoriasis as skin reaction to systemic psoriatic process SPP. Y-model of pathogenesis.

Presentation about theoretical research. Version e2.1.

**Mikhail Peslyak**

This presentation is based on e-books:

Model of pathogenesis of psoriasis. Part 1. Systemic psoriatic process. Moscow, MYPE, 2012, 84 p., ISBN 9785905504020

Model of pathogenesis of psoriasis. Part 2. Local processes. Moscow, MYPE, 2012, 110 p., ISBN 9785905504044

These e-books are freely accessible at www.psorias.info

On many slides links to connected sections of these e-books are existed.
Put this pdf-file and pdf-files of e-books in one directory that these links were functional.

# Theses



In Y-model the main role play small intestine colonization by Gram+ psoriagenic bacteria PsB and Gram(-) TLR4-active bacteria and its hyperpermeability for bacterial products.

PsB are E.faecalis, Str.pyogenes, VGS, Str.agalactiae and some of Bifidobacterium spp. PsB possess PG-Y - peptidoglycan A3alpha containing interpeptide bridges IB-Y (i.e. L-Ala(2-3) and-or L-Ala-L-Ser).

SPP central subprocess is PAMP-nemia providing chronic increased kPAMP-load on blood phagocytes.

kPAMP are key PAMP. The major kPAMP are LPS and PG (including PG-Y). This kPAMP-load provides in blood flow the occurence of fraction of tolerized monocytes Mo-T and dendritic cells DC-T. The chemostatuses of tolerized Mo-T and DC-T are similar to nonactivated ones.

The part of Mo-T and DC-T appears to be (PG-Y)-carriers and are designated as Mo-R and DC-R (reprogrammed and repleted).

SPP severity depends of total volume of (PG-Y)-carriage of blood Mo-R and DC-R. SPP severity predetermines possibility of psoriasis initialization and maintenance, because Mo-R and DC-R participate in homeostatic and inflammatory renewal of pool of dermal Mo and DC.

Y-antigen is a part of interpeptide bridge IB-Y. As blood Mo-R and DC-R contain Y-antigen, than getting to inflamed derma, they can be transformed in mature maDC-Y. Further, maDC-Y present Y-antigen to TL-Y (Y-specific T-lymphocytes) and activate them. Skin immune system can interpret Y-antigen presentation as a sign of external PsB-infection and activate one of protection mechanisms – epidermal hyperproliferation.

Psoriatic plaque can be initiated only during dermal inflammatory process LP2 causing both innate and adaptive response. Y-priming level (TL-Y concentration in prepsoriatic derma and lymph nodes) also important.

The severity of plaque is defined by intensity of Y-antigen income into derma (inside Mo-R and DC-R). Its severity is aggravated by LP2-inflammation if it persists after plaque initiation.

New Mo-R, DC-R and TL-Y are attracted from blood flow to plaques, and so support vicious cycles. At decrease of SPP severity, vicious cycles weaken and remission of plaques takes place, up to their complete disappearance.

# Methods and Objective



Publications with subject of examination of GIT and hepatobiliary system, investigation of intestine and biliary microflora or antiendotoxic and antistreptococcal immunity in psoriasis were searched and analyzed.

Search and analysis of works where well-based models of pathogenesis of psoriasis are offered have been carried out. Experimental works supporting these models have been studied.

Publications investigating the condition of prepsoriatic skin and events initiating psoriatic plaque (Koebner's effect) have been analysed.

Publications were searched in **Medline** and **Embase**.

Russian publications were searched in **Central Scientific Medical Library** and in **Scientific Electronic Library**.

**The main objective is construction of a modern systemic model of pathogenesis of psoriasis.**

# Main pathogenesis models

Link to connected section in e-book


Systemic **BF-model** suggested by Barbara Baker and Lionel Fry at 2006-7. The antigenic role of streptoccocal peptidoglycan outside skin (gut, tonsils, blood flow) and inside psoriatic skin suggested for the first time.
Faculty of Medicine, Imperial College, London, UK.

There are two modern local models:

Link to section in e-book

**N-model** suggested by Frank Nestle with co-workers at 2009-11.
St. John's Institute of Dermatology, King's College London and NIHR Biomedical Research Centre, London, UK.

**GK-model** suggested by Emma Guttman, James Krueger with co-workers at 2011.
Laboratory for Investigative Dermatology, The Rockefeller University, New York, USA.

# Y-model is systemic model of pathogenesis



- Y-model contains well-known and new fragments.
  New fragments based on recently discovered and researched facts.
  Some of new fragments are hypothetical (marked by ?).

- Psoriasis is considered as skin reaction to systemic psoriatic process (SPP). SPP acts outside of skin (intestine, hepatobiliary system, blood flow). SPP severity defines psoriasis severity.

- SPP partial based on BF-model. Some local fragments of Y-model are formulated as in N-model and/or in GK-model.

There are two parts of this report:

Part 1. Systemic psoriatic processes and its subprocesses.

Part 2. Local processes in skin before, during and after psoriatic plaque initiation.


# Y-model. Part 1. Systemic psoriatic process and its subprocesses.

# SPP. Basic researches.

Link to connected section in e-book


**Many of psoriatic patients had malabsorption syndrome.**
Eugeny Kharkov with co-workers (from 2005 till now).
Krasnoyarsk state medicine university, Krasnoyarsk, Russia.

Link to section in e-book

☼☼☼☼☼☼☼☼☼

**Majority of patients with psoriasis had SIBO (small intestine bacterial overgrowth).** Natalia Potaturkina-Nesterova with co-workers (2007-9).
Ulyanovsk State University, Ulyanovsk, Russia.

☼☼☼☼☼☼☼☼☼

**Majority of psoriatic patients had high blood LPS-level.**
Zuhra Garaeva with co-workers (2005-7).
Kazan Medicine Academy, Kazan, Russia.

☼☼☼☼☼☼☼☼☼

**Phagocytes tolerization (reprogramming) and their properties.**
Robert Sabat and Kerstin Wolk with co-workers (2000-2005)
University Hospital Charité, Berlin, Germany.
Jean-Marc Cavaillon with co-workers (from 2004 till now).
Institut Pasteur, Paris, France.

Link to section in e-book

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**Systemic model of pathogenesis. The antigenic role of streptoccocal peptidoglycan outside skin (gut, tonsils, blood flow) and inside psoriatic skin.** Barbara Baker and Lionel Fry (2006-7).
Faculty of Medicine, Imperial College, London, UK.

Link to section in e-book

# Bacteria and bacterial products (symbols)

Link to connected section in e-book



| | |
|---|---|
| PG | PG = any peptidoglycan (in particular PG-Y) |
| Y-antigen | Y-antigen = part(s) of interpeptide bridge IB-Y ? |
| PG-Y | PG-Y = peptidoglycan A3alpha with interpeptide bridges IB-Y (but can contain and others also) |
| PsB | PsB = psoriagenic bacteria = Gram+ bacteria with peptidoglycan PG-Y. |

| | |
|---|---|
| LPS | LPS = lipopolysaccharide, free and bound in complexes with LBP, sCD14, etc. |
| | Gram(-) TLR4-active bacteria |
| | Gram+ and Gram(-) bacteria - intestine commensals |
| | PsBP = vital activity and/or degradation products of PsB |

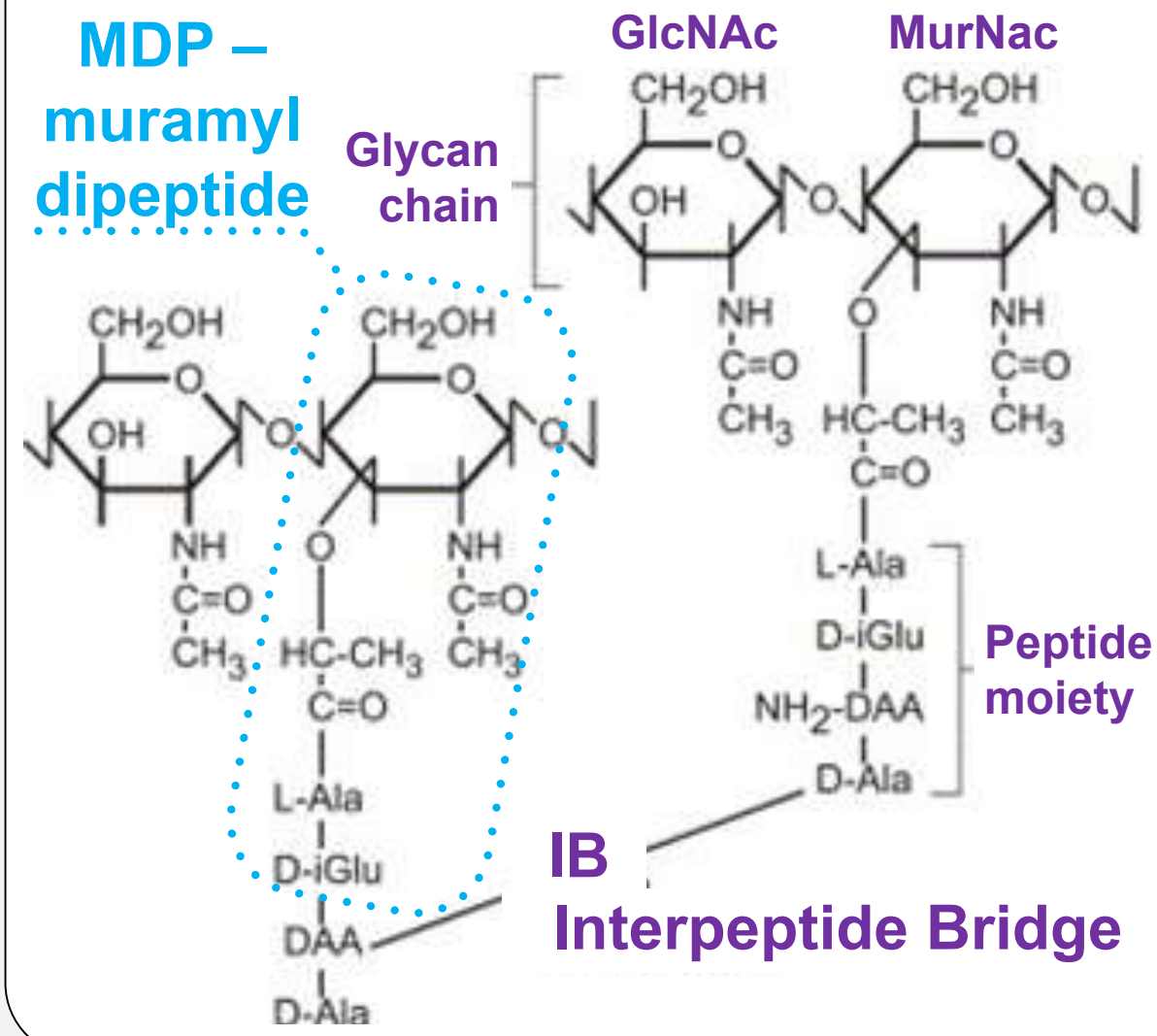
# PG structure and PsB

Link to connected section in e-book



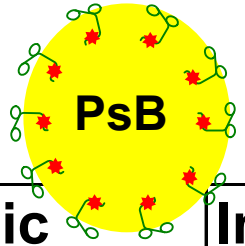
PG

## Peptidoglycan (any)




PG-Y

## Peptidoglycan with IB-Y




| Psoriagenic bacteria PsB | Interpeptide Bridge |
|---|---|
| Str.pyogenes | L-Ala(2-3) or L-Ala-L-Ser |
| Str.agalactiae | L-Ala(2) or L-Ala-L-Ser |
| E.faecalis | L-Ala(2-3) |
| Some of VGS (viridans group streptococci) | L-Ala(1-3) |
| Some of Bifidobacterium spp. | L-Ala(2-3) or L-Ala-L-Ser |

# Small intestine.
# Hyperpermeability & Changed microflora.

Link to connected section in e-book



In Y-model the main role play two origin casual subprocesses in small intestine:

SP1. Hyperpermeability for bacterial products.

Link to section in e-book

SP2. Growth of populations of Gram+ (incl. psoriagenic PsB) and Gram(-) TLR4-active bacteria.

Link to section in e-book

These two subprocesses (with others) support

SP4. PAMP-nemia = Endotoxinemia + PG-nemia.

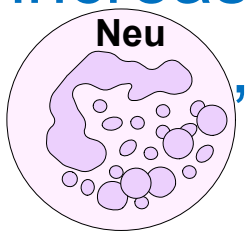
Link to section in e-book

**kPAMP (key PAMP) are**

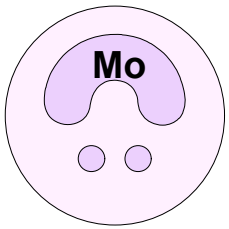
**LPS (lipopolysaccharide) and**

**PG (peptidoglycan).**

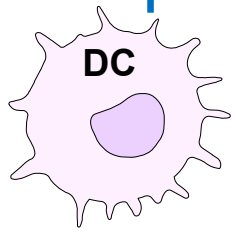
**PAMP-nemia** is increased **kPAMP-level** in blood flow and increased **kPAMP-load** on blood phagocytes: neutrophiles Neu




, monocytes Mo




, dendritic cells DC



# Immune cells (symbols)

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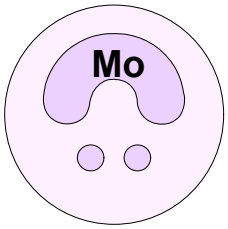
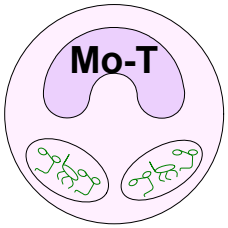
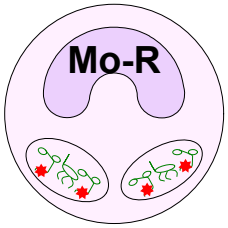
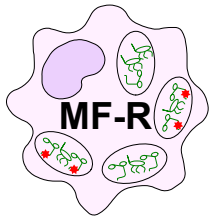
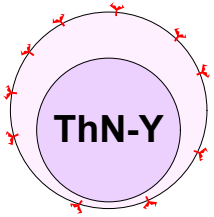
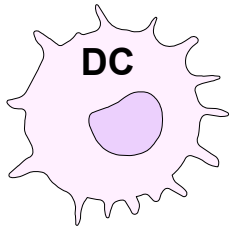
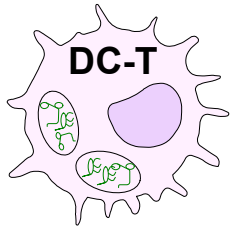
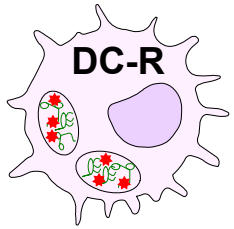
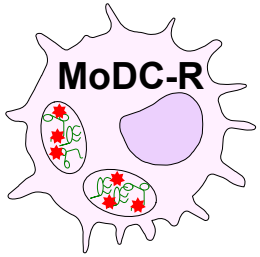
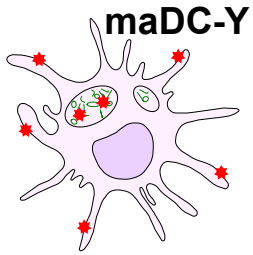
| | |
|---|---|
|   | Mo = monocytes |
|   | Mo-T = tolerized monocytes. They are kPAMP-carriers. |
|   | Mo-R = PG-Y(+)Mo-T |
|   | MF-R = macrophages, derived from Mo-R |
|   | ThN-Y = Y-specific Th1, Th17 and Th22 Link to section in e-book |

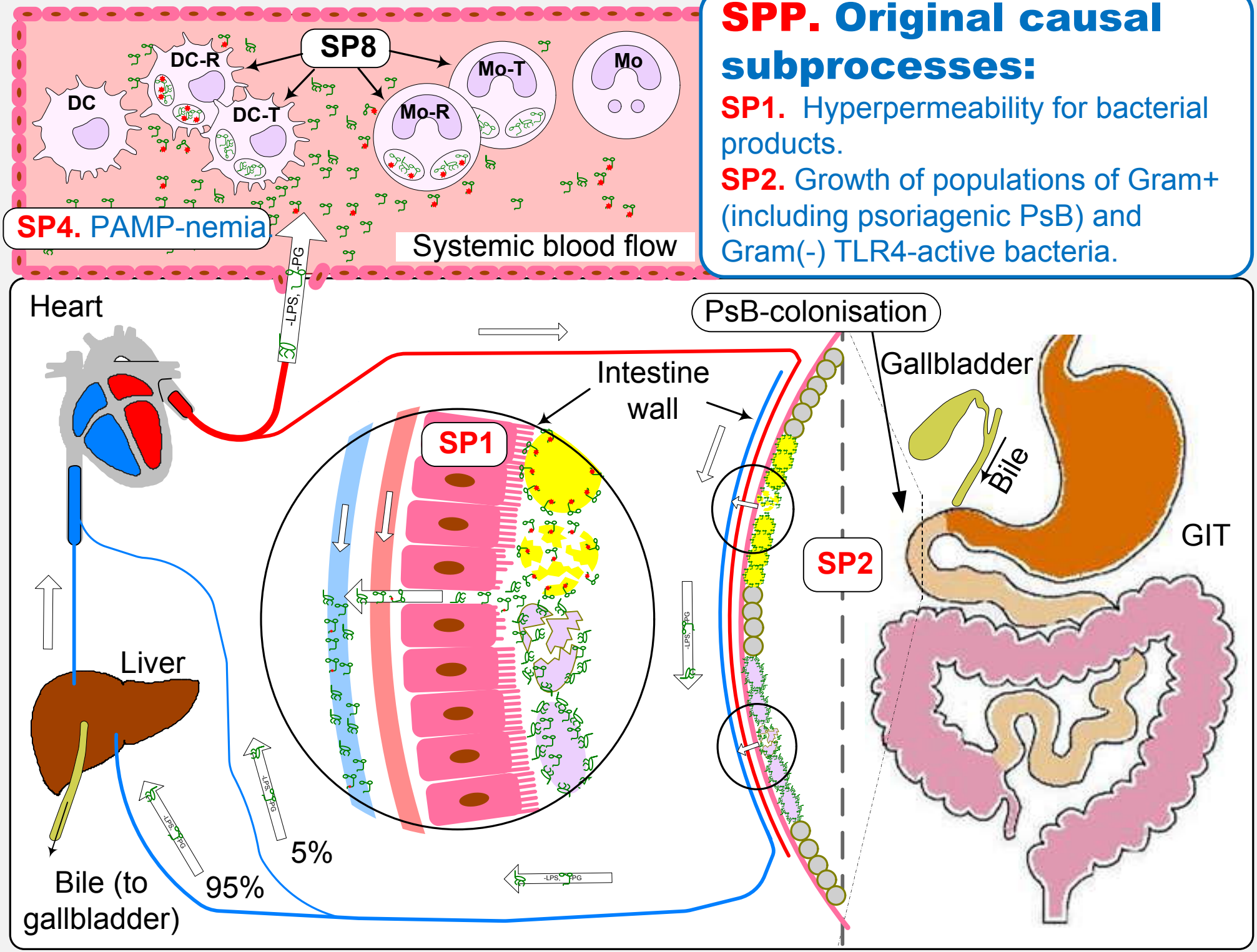
| | |
|---|---|
|   | DC = dendritic cells |
|   | DC-T = tolerized dendritic cells. They are kPAMP-carriers. |
|   | DC-R = PG-Y(+)DC-T |
|   | MoDC-R = dendritic cells, derived from Mo-R |
|   | maDC-Y = mature dendritic cells, presenting Y-antigen |

Link to connected section in e-book

# SPP. Original causal subprocesses:

**SP1.** Hyperpermeability for bacterial products.

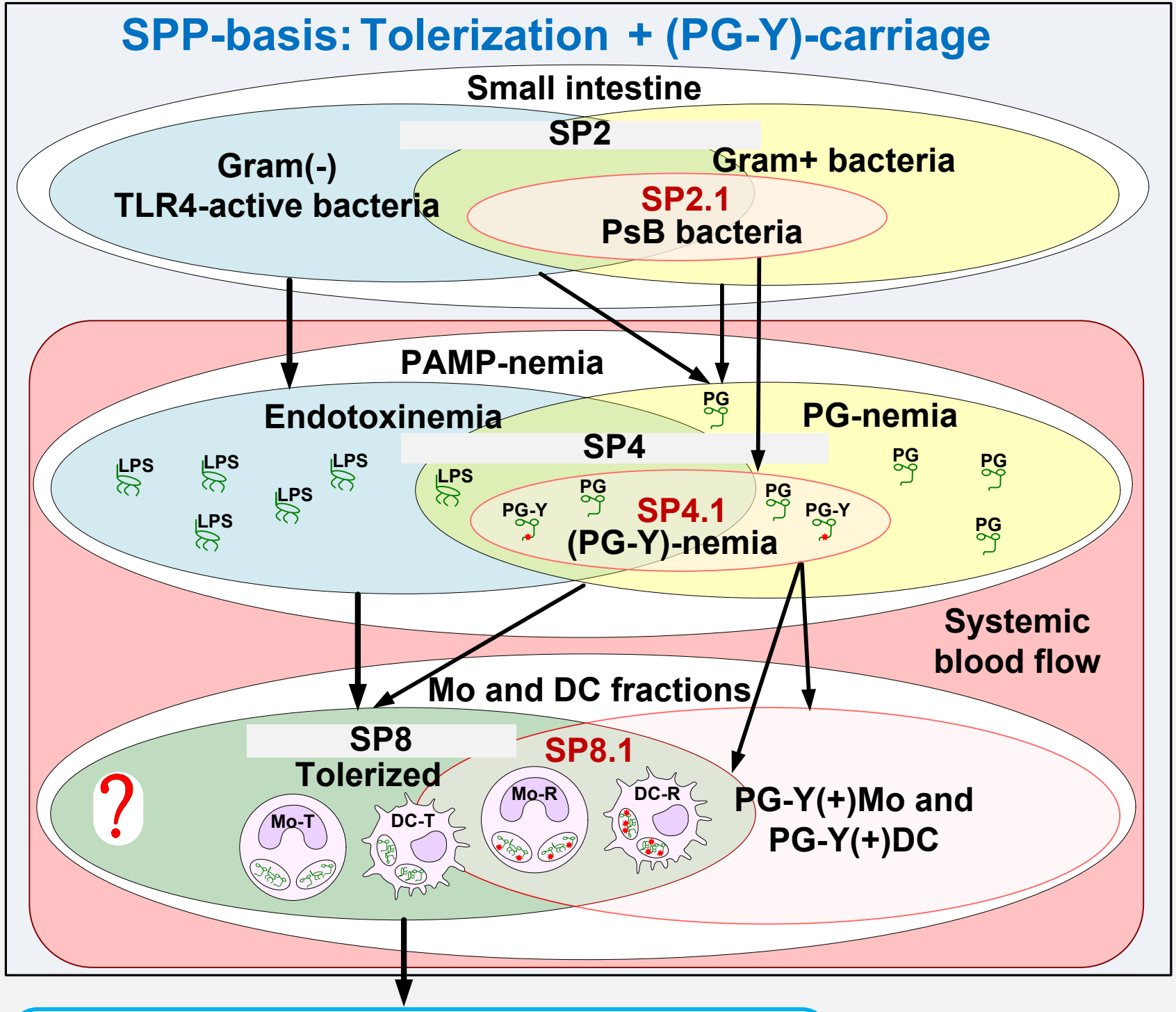
**SP2.** Growth of populations of Gram+ (including psoriagenic PsB) and Gram(-) TLR4-active bacteria.



# SPP-basis: Tolerization + (PG-Y)-carriage

Link to connected section in e-book






LP1.1. Attraction of Mo and DC, Mo-T and DC-T (incl. Mo-R and DC-R) from blood flow.

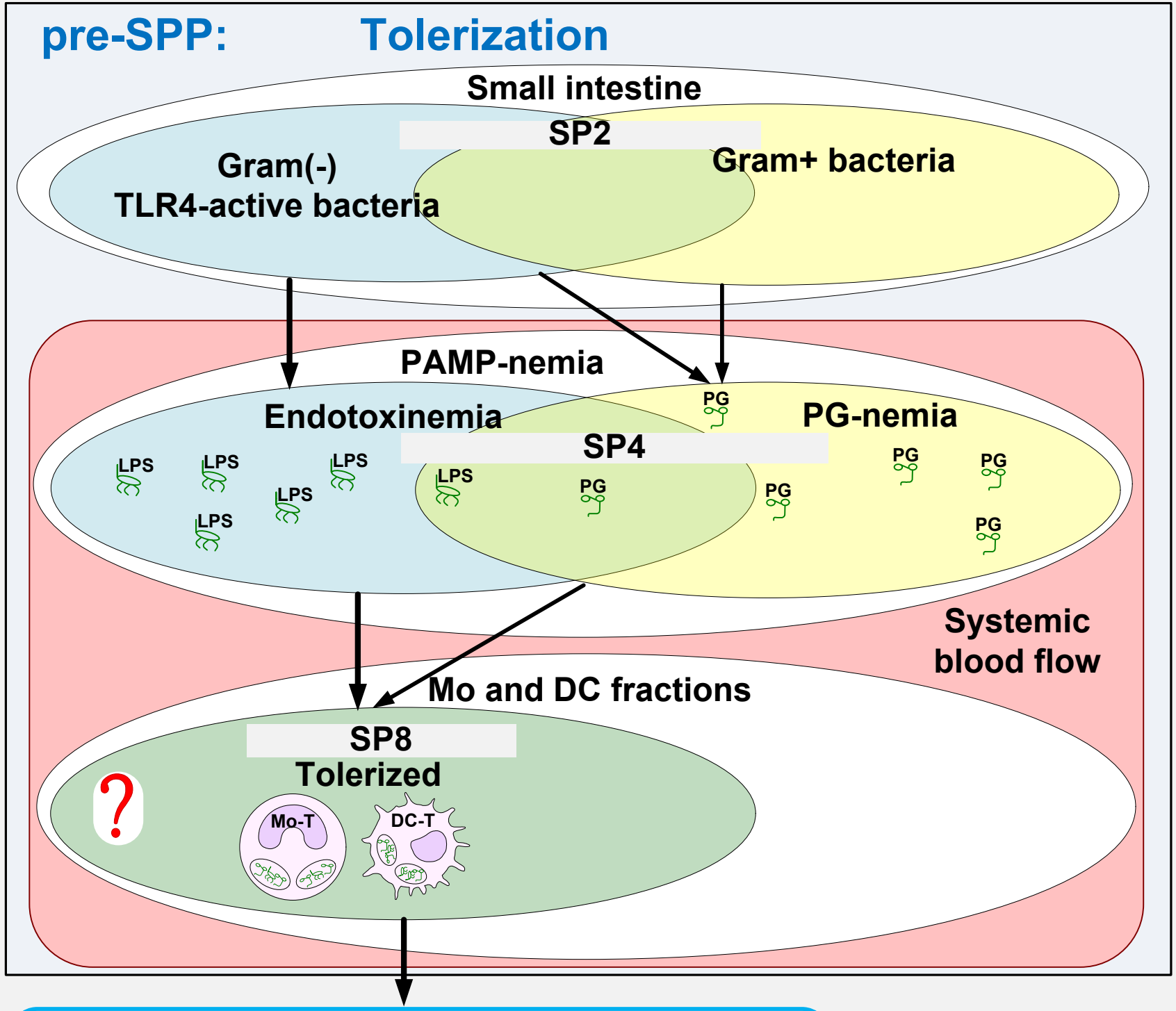
## Two components of SPP-basis: tolerization of phagocytes and their (PG-Y)-carriage.

Mo-R = PG-Y(+)Mo-T
DC-R = PG-Y(+)DC-T

Subfractions of Mo-R and DC-R may to exist (SP8.1) only when these two components operate together.

**SPP operates only if SP8.1 operates.**

# pre-SPP: Tolerization




LP1.1. Attraction of Mo and DC, Mo-T and DC-T from blood flow.

## Two components of SPP-basis: tolerization of phagocytes and their (PG-Y)-carriage.

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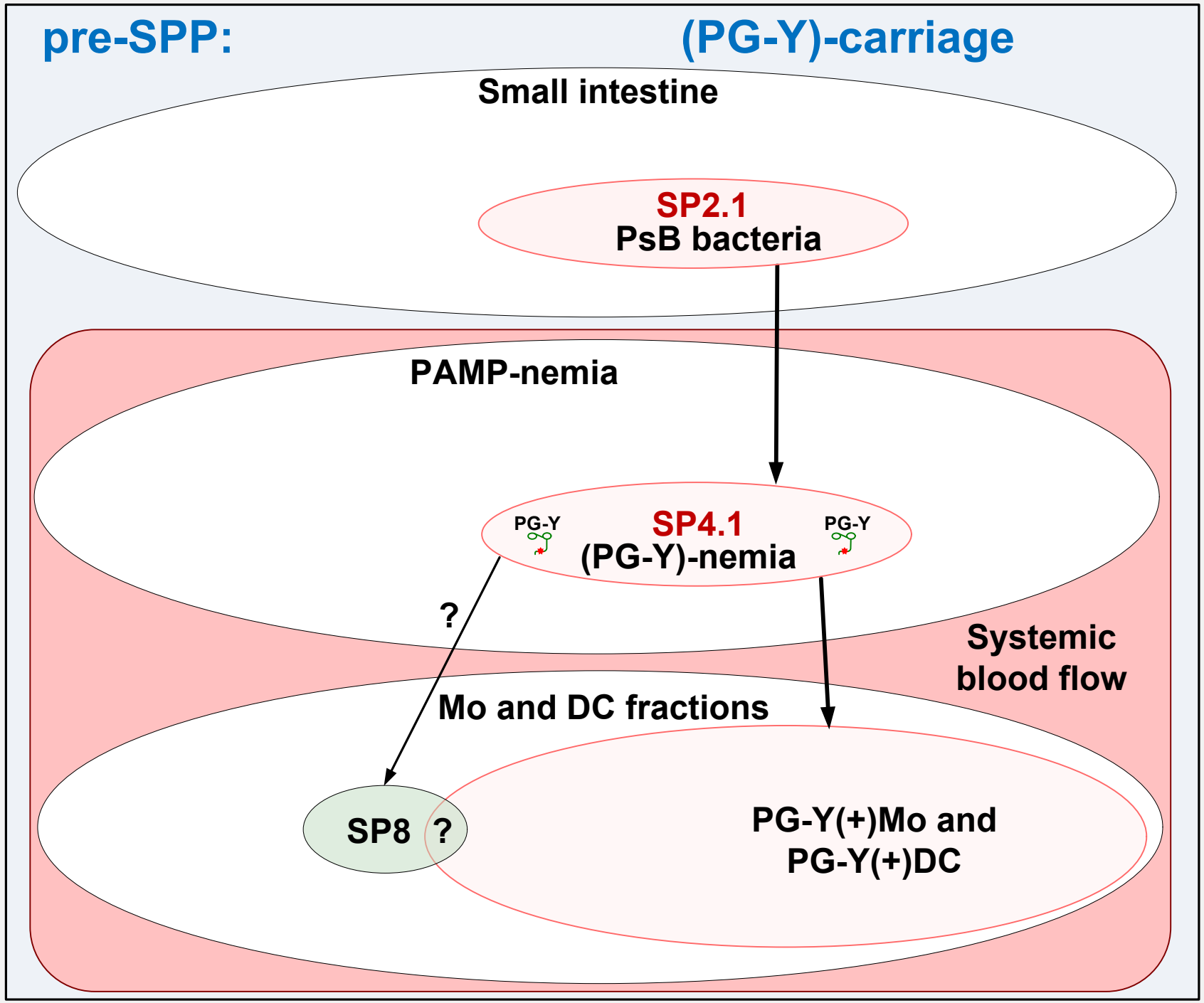



# Two components of SPP-basis: tolerization of phagocytes and their (PG-Y)-carriage.

Mo-R = PG-Y(+)Mo-T
DC-R = PG-Y(+)DC-T

Subfractions of Mo-R and DC-R may to exist (SP8.1) only when these two components operate together.

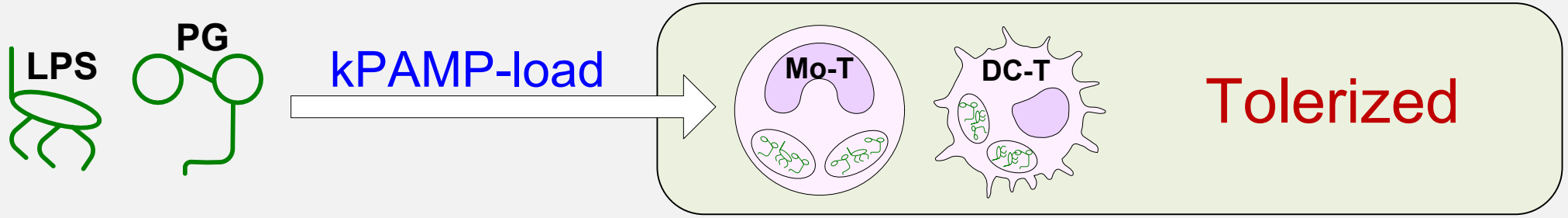
**SPP operates only if SP8.1 operates.**

# Mo and DC.
# Tolerization + (PG-Y)-carriage.

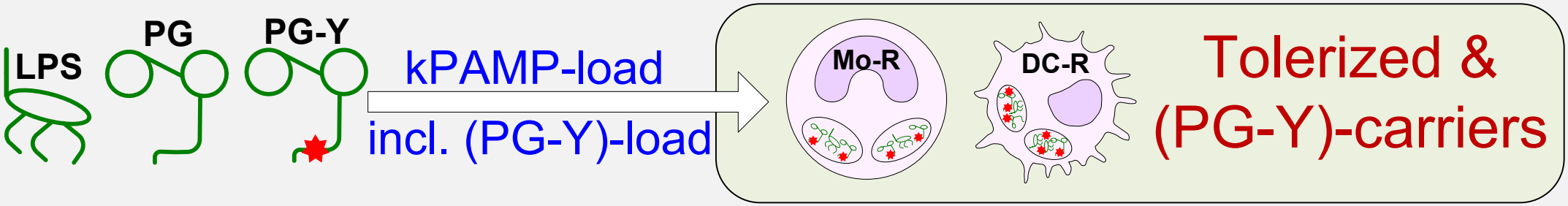
Link to connected section in e-book



? Chronic kPAMP-load provides in blood flow the occurence of fraction of tolerized Mo-T and DC-T.




The part of Mo-T and DC-T appears to be (PG-Y)-carriers and are designated as Mo-R and DC-R.




SPP severity is proportional to total volume of (PG-Y)-carriage of blood Mo-R and DC-R.

# Distribution of stay time of monocytes in blood flow



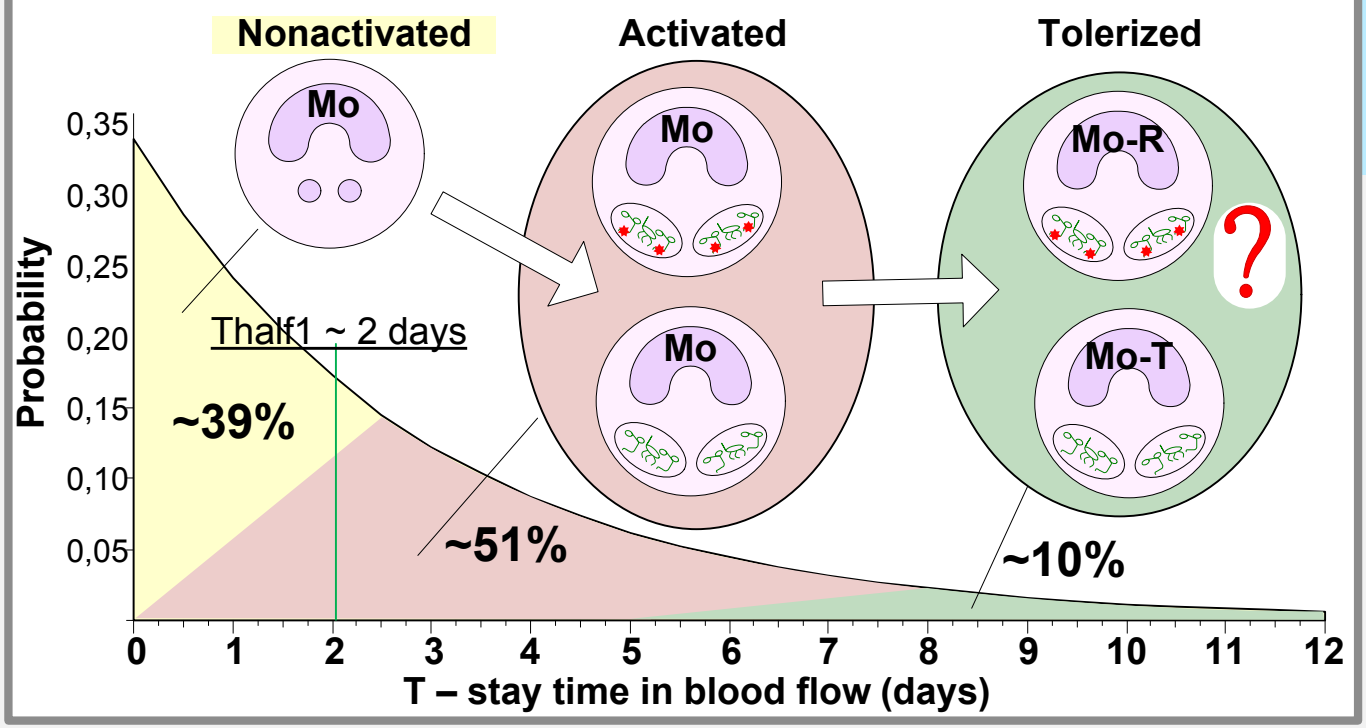
Link to connected section in e-book

**How tolerized fraction is formed?**

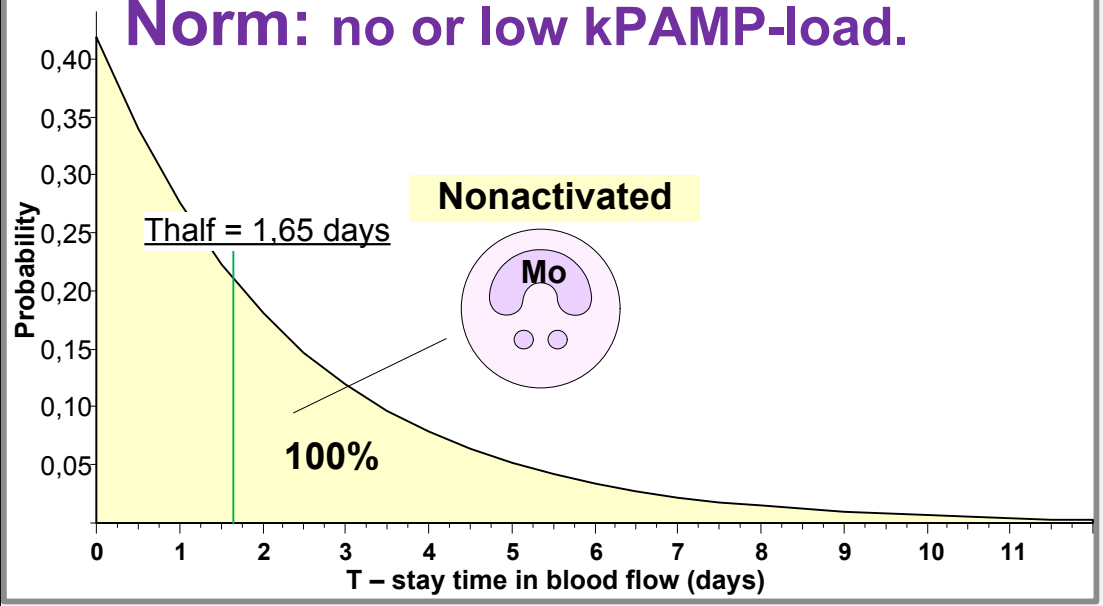
**Samples of fractionation: at SPP (Systemic Psoriatic Process); at CARS (Compensatory Anti-inflammatory Response Syndrome).**

**Is SPP a weak CARS?**

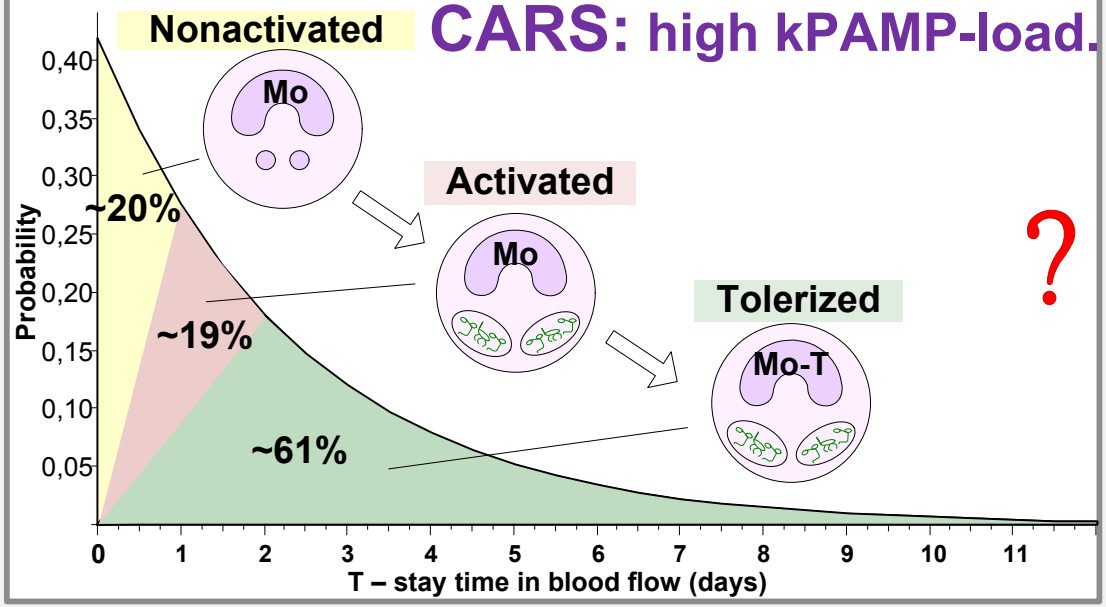
## SPP: increased kPAMP-load.



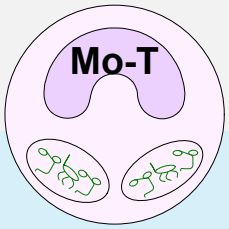

## Norm: no or low kPAMP-load.

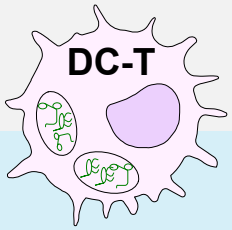



## CARS: high kPAMP-load.



# Tolerized Mo-T and DC-T




Link to connected section in e-book



## Are lowered

- Secretion of proinflammatory cytokines (TNF-alpha, IL-1beta, IL-12, etc.) after repeated PAMP-load.
- Expression of HLA-DR, CD74, HLA-DM, CD58 (LFA-3) and CD86 etc.
- Production and level of intracellular proteins cathepsin S and legumain, which are responsible for splitting and processing of antigens.
- Production, transport and expression of MHC II
- Ability to presentation of antigens and activation of T-lymphocytes.

**Raised** level of intracellular protein **IRAK-M**, the general manager of tolerization.

**Property 2.**
They are kPAMP-carriers.

**Ability to fast loss of tolerance**
(to be deprogrammed)
under the influence
of cytokines-deprogrammers
IFN-gamma, GM-CSF
and (indirectly) IL-12.

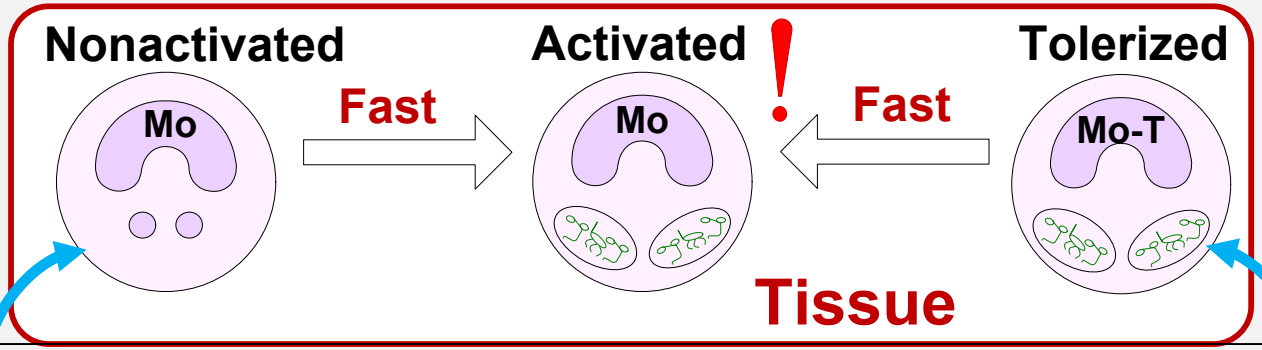
**Property 1.**
Their chemostatuses (ranges of expressed chemokine receptors) are similar to nonactivated ones.

**DC-T - yes**
**Mo-T - ?**

# CD14+CD16+Mo transformation and chemostatus

Link to connected section in e-book



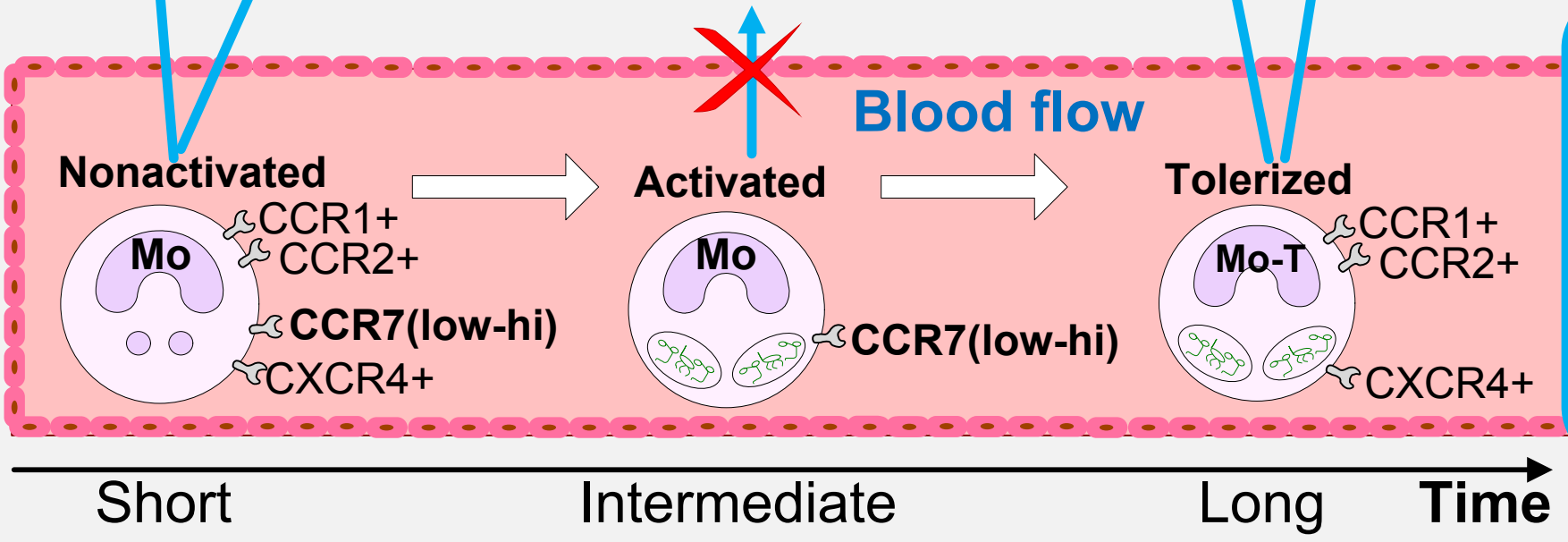



## Inflammation

Cytokines-deprogrammers GM-CSF, IFN-gamma are in abundance.
kPAMP-load is possible.


## Homeostasis

Cytokines-deprogrammers GM-CSF, IFN-gamma are absent.
kPAMP-load is absent.




?

**Property 1.** Chemostatus of Mo-T is similar to nonactivated.

Short — Intermediate — Long — **Time**

**Expected stay time in blood flow under chronic kPAMP-load.**

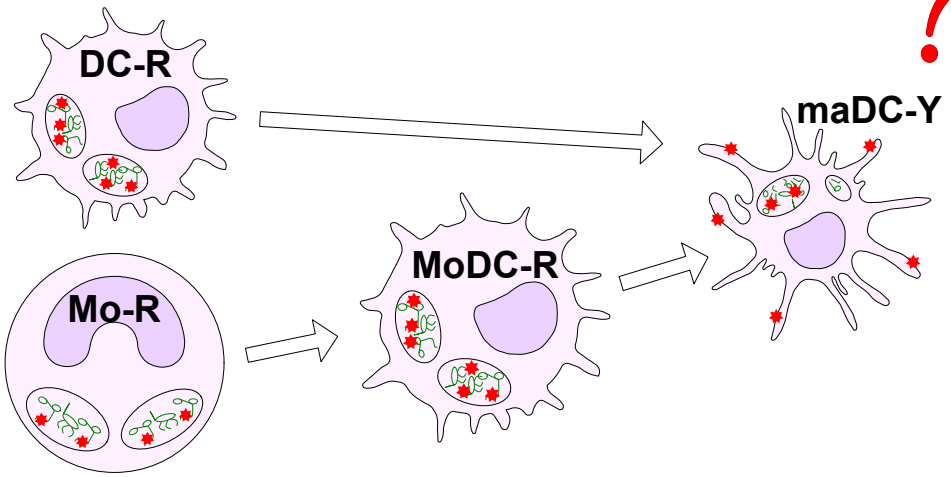
# Y-model. Part 2. Local processes in skin before, during and after single psoriatic plaque initiation.

# Mo-R and DC-R transformation in derma

Link to connected section in e-book



If tolerized Mo-R and DC-R getting to inflamed derma – they can be transformed into mature maDC-Y, presenting Y-antigen. ?




Because of their ability to fast loss of tolerance (to be deprogrammed). Conditions for this occur only during inflammatory process(es), when cytokines-deprogrammers IFN-gamma, GM-CSF and IL-12 are in abudance.

These conditions are during PLS-inflammation (incl. adaptive response), when plaque already exists, but what is the cause of such conditions before plaque start? Kebnerization.

**NLS** = non-lesional skin
**PLS** = psoriatic lesional skin
**LP2** = dermal initiating and aggravating process – the reason of koebnerization

**Inflammations in NLS or in PLS**

- LP2-inflammation in NLS only (LP2 operates, but no plaque present yet).
- LP2- and PLS-inflammation coexistence (LP2 operates and plaque exists).
- PLS-inflammation only (LP2 ended, but plaque exists).

# Phases of psoriatic plaque development

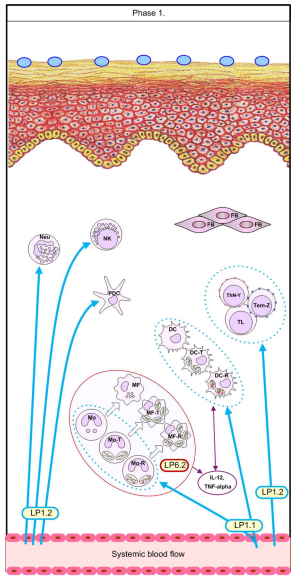
Link to connected section in e-book



Prepsoriasis (NLS)

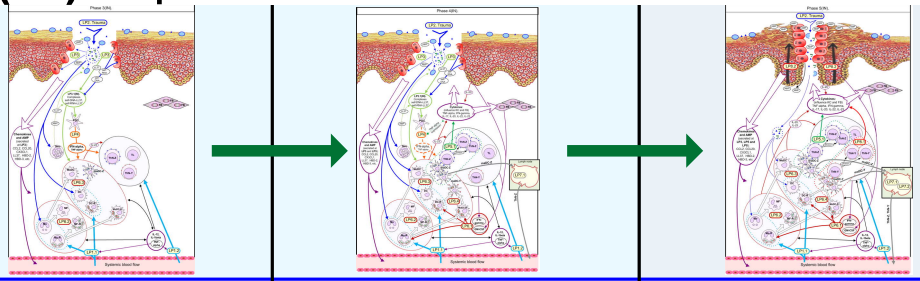
Psoriasis (PLS)

| 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|
| Homeostasis. LP2 is absent. This phase is common for any LP2. | Koebnerization. Phase starts when LP2 (initiating and aggravating process) and LP3 (innate response against LP2) start. | Phase starts when LP4 (trigger for LP5) starts. | Phase starts when LP5 (adaptive response against LP2) starts. | Phase starts when LP8 (false adaptive response to imaginary PsB-infection) starts. | Phase starts when LP2, LP3 and LP5 end. Phase is common for any LP2. LP8 (false adaptive response to imaginary PsB-infection) became self-sufficient. ? |



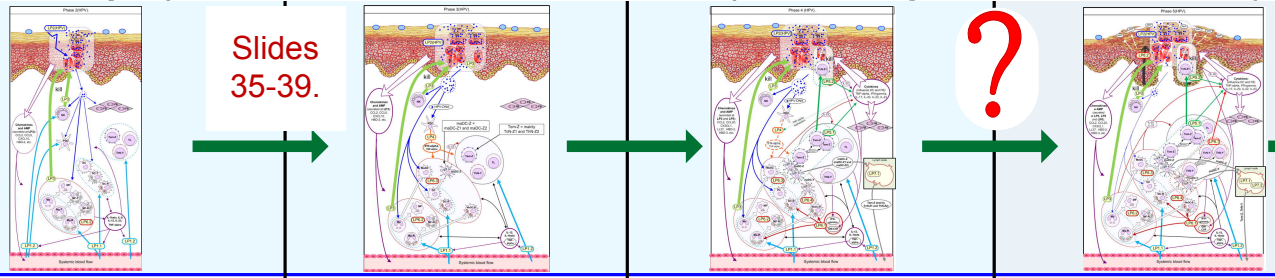

**LP2(IN).** Open trauma of derma

Slides 31-33 and 39.

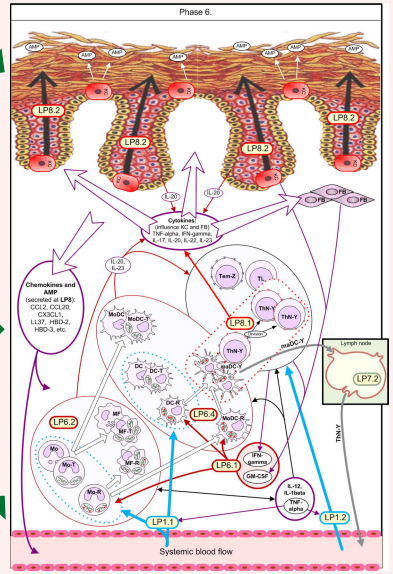


**LP2(HPV).** (Human Papilloma Virus)-carriage of keratinocytes

Slides 35-39.



**Others LP2:** Skin PsB-infection; S. aureus infection; Combustion; Contact dermatitis; Malassezia Species infection; Candida Albicans infection; etc.

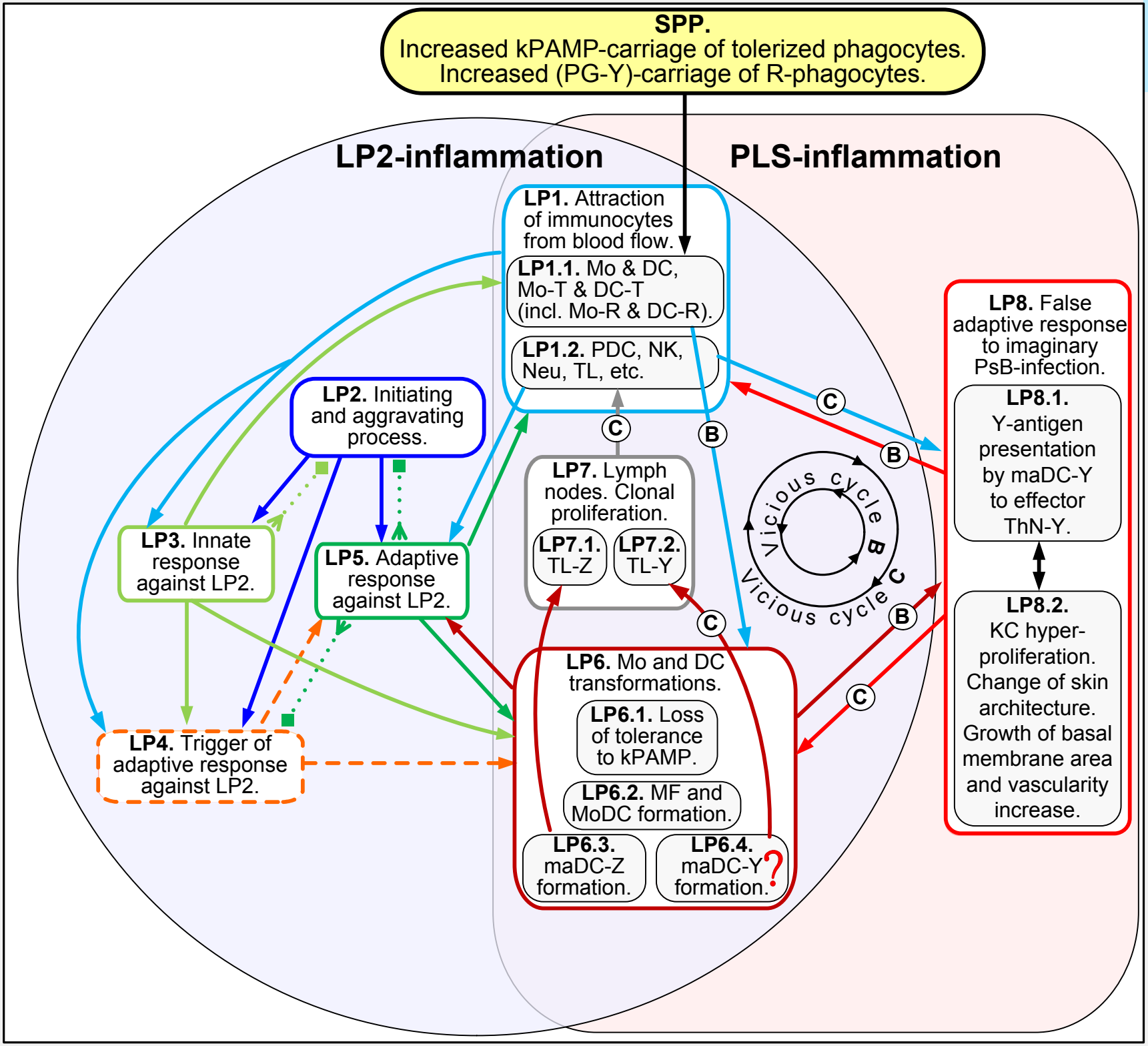



Phase 6 on slide 39.

Link to connected section in e-book

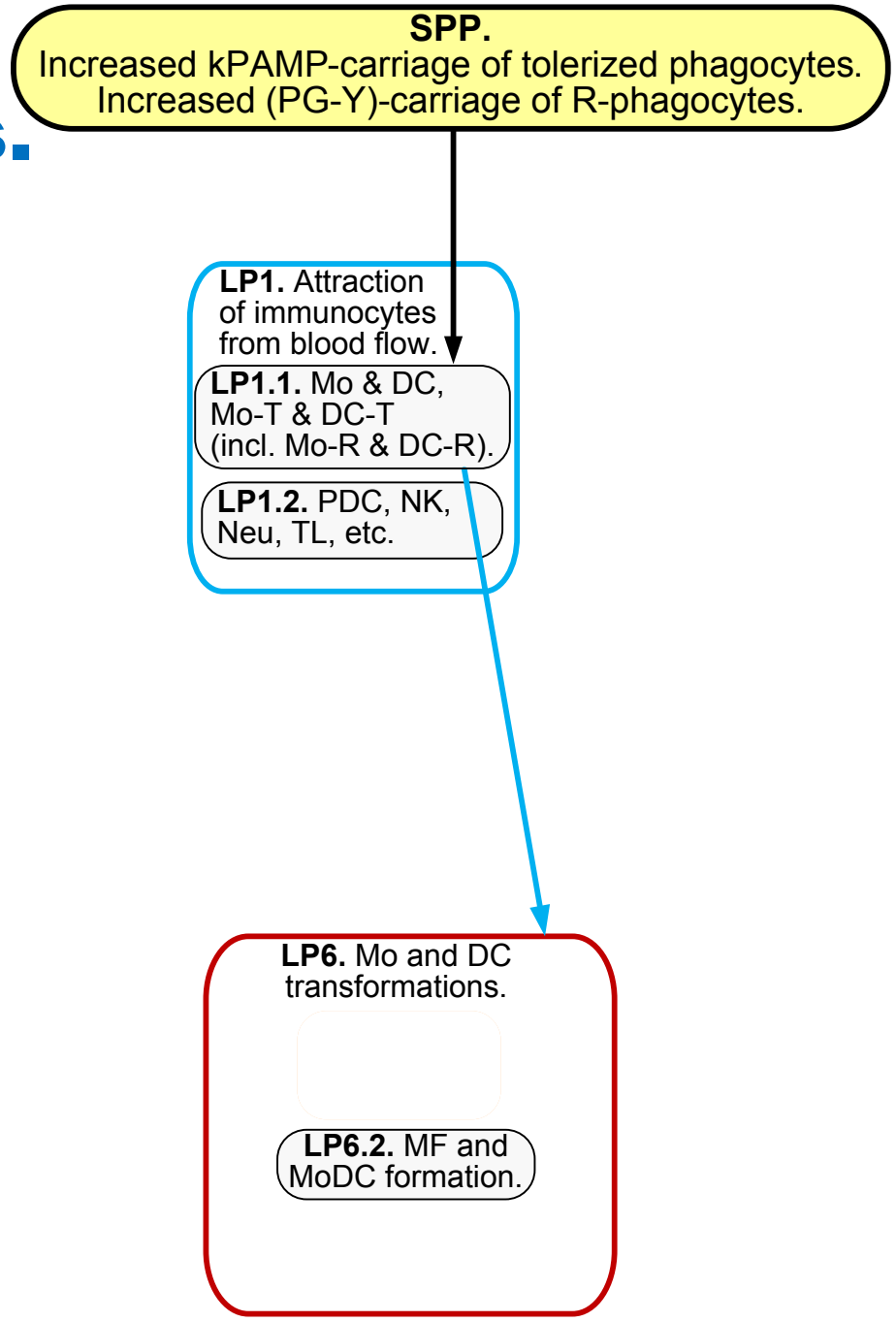


# Y-model. Interaction of local processes.




The most important causal dependencies are represented by color arrows.
The color of an arrow depends on the color of a causative process.

# Phase 1. Prepsoriasis.




Homeostasis.
LP2 is absent.
This phase is common for any LP2.

Link to connected section in e-book


# Y-model. Interaction of local processes.

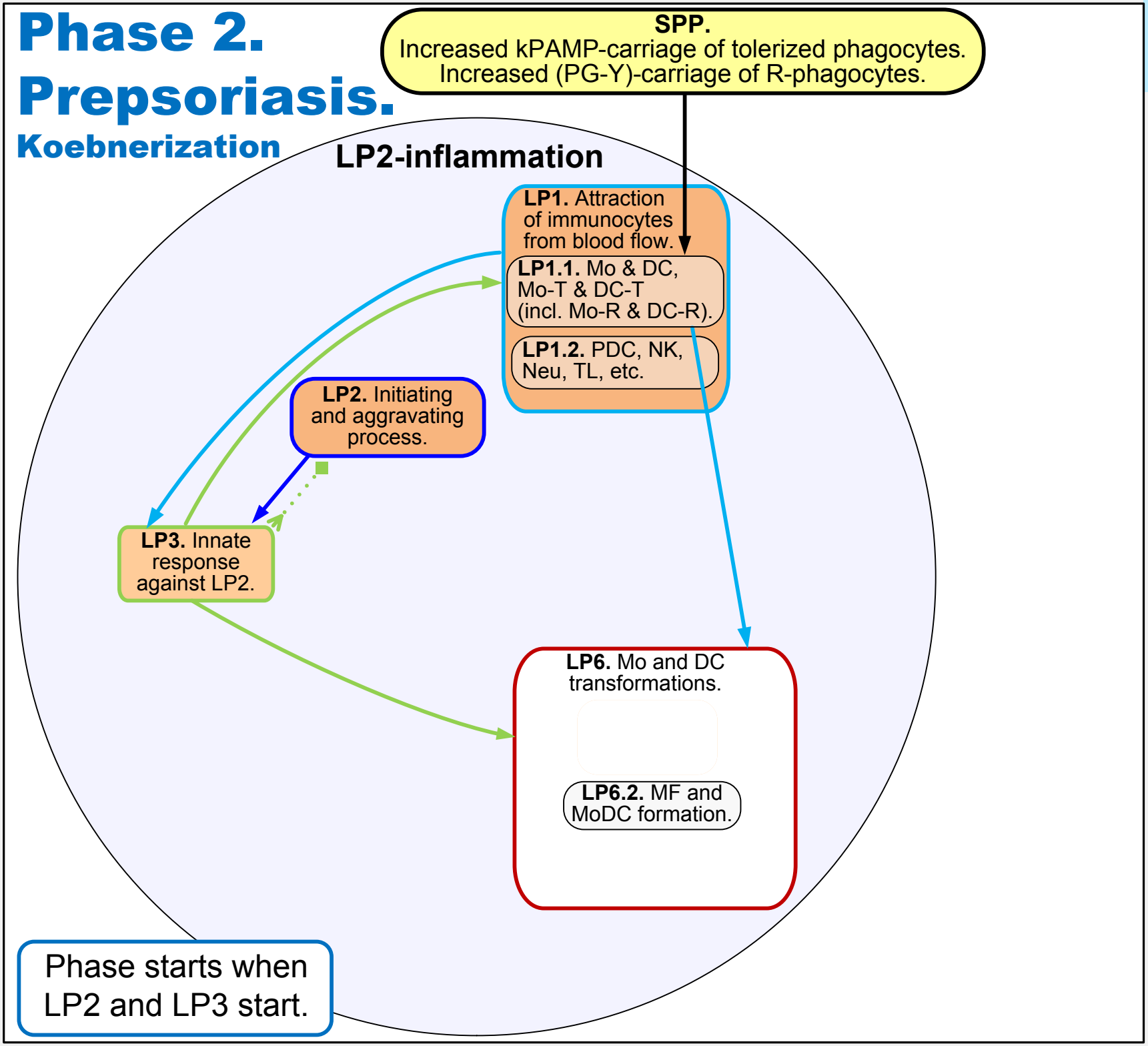
**Phases of psoriatic plaque development.**

Dotted arrows – suppression.

Process intensity:
white – weak;
beige – average inflammatory;
pink – high inflammatory;

# Phase 2. Prepsoriasis.

## Koebnerization




Phase starts when LP2 and LP3 start.

Link to connected section in e-book



# Y-model. Interaction of local processes.

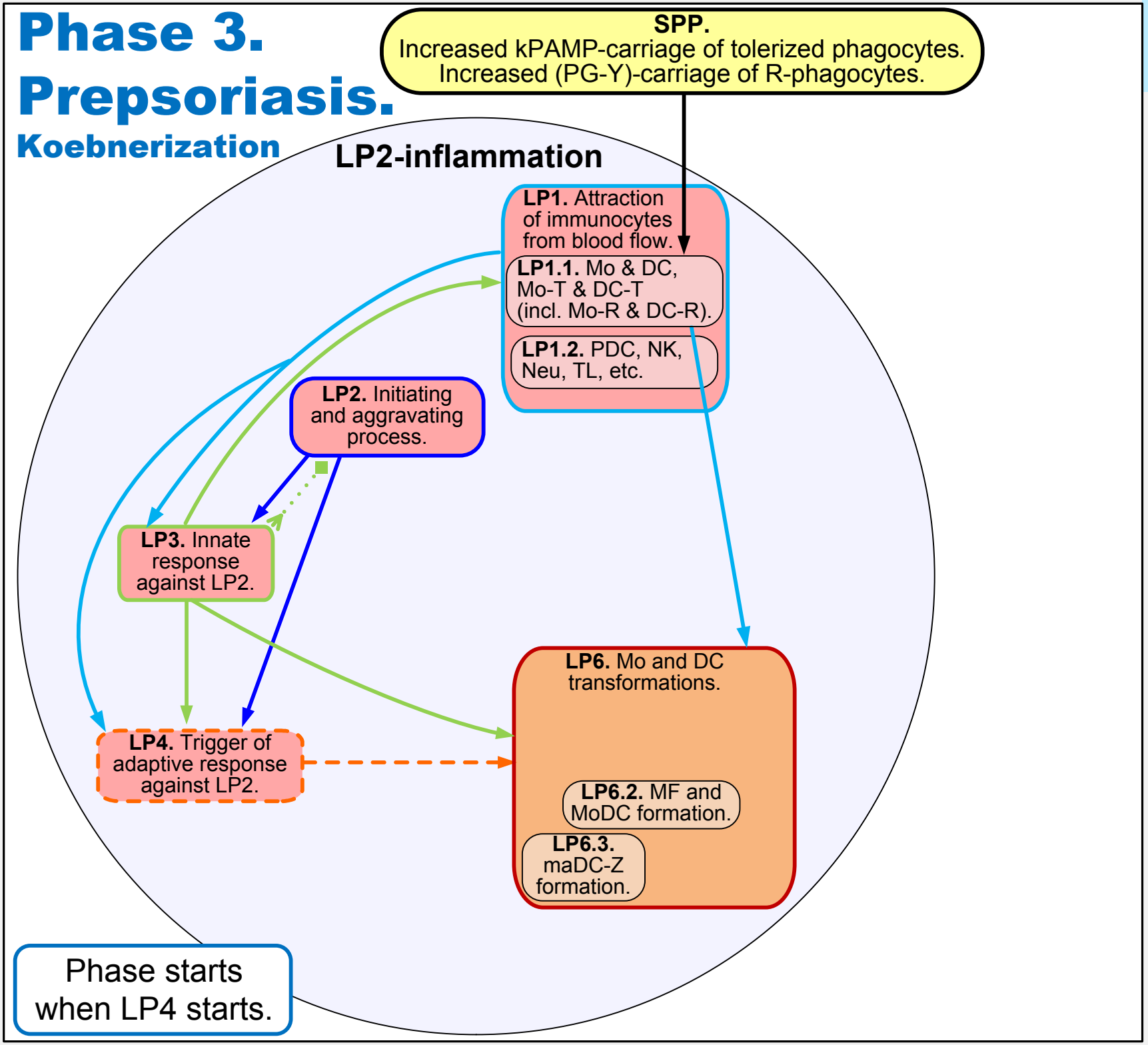
**Phases of psoriatic plaque development.**

Dotted arrows – suppression.

Process intensity:
white – weak;
beige – average inflammatory;
pink – high inflammatory;

# Phase 3. Prepsoriasis.

## Koebnerization




Link to connected section in e-book



# Y-model. Interaction of local processes.

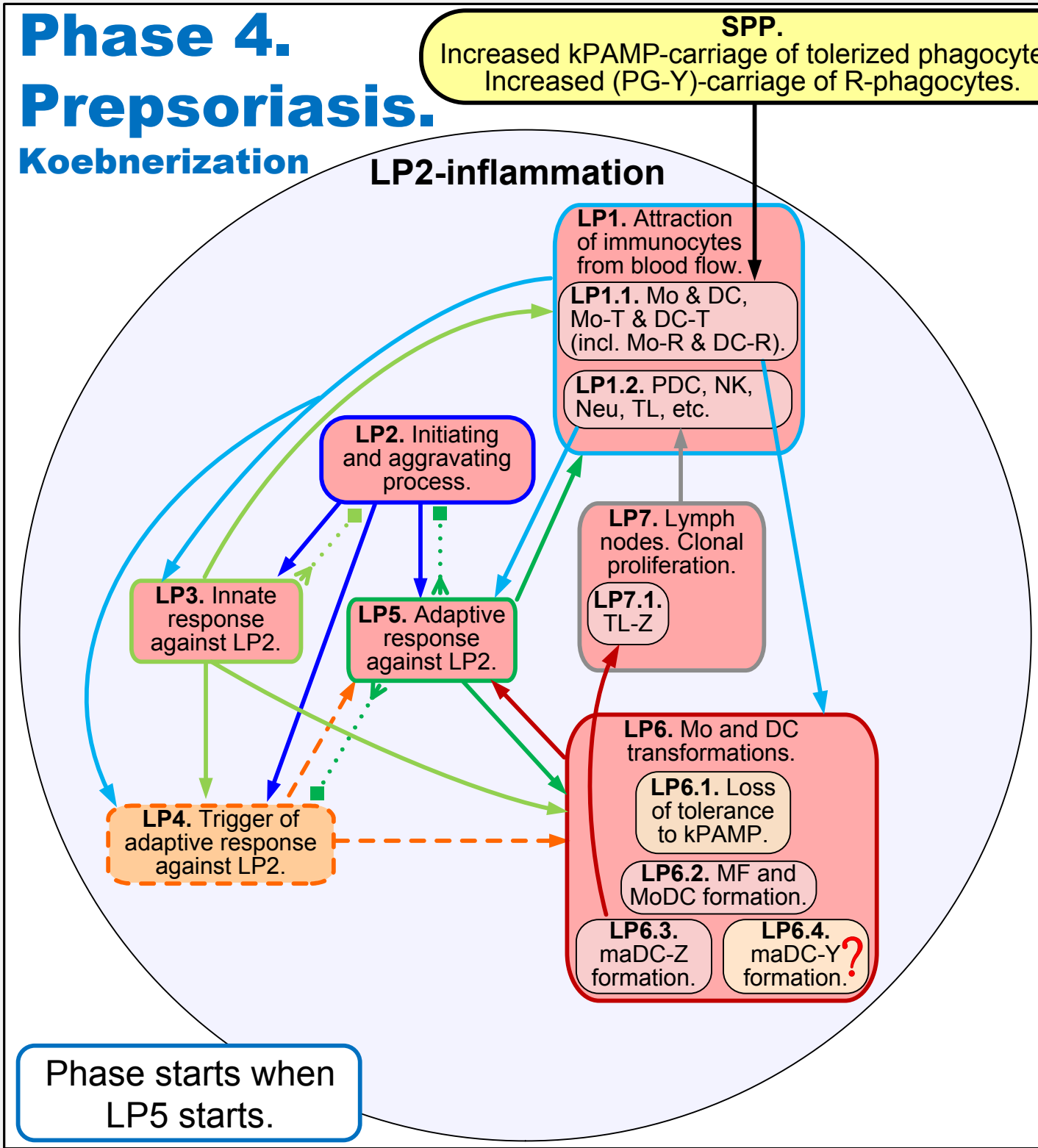
**Phases of psoriatic plaque development.**

Dotted arrows – suppression.

Process intensity:
white – weak;
beige – average inflammatory;
pink – high inflammatory;

# Phase 4. Prepsoriasis.

## Koebnerization




Link to connected section in e-book

27

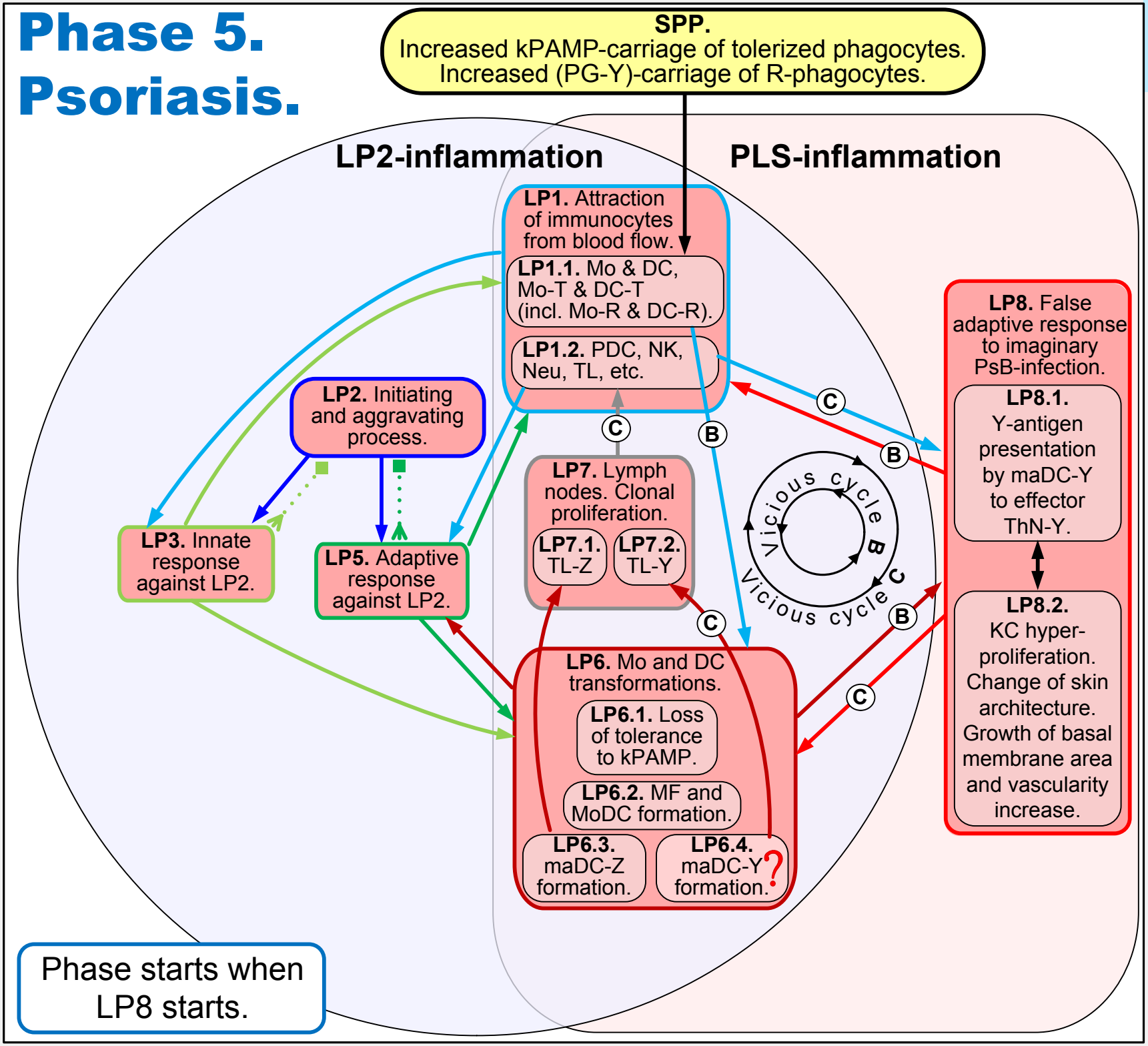
# Y-model. Interaction of local processes.

**Phases of psoriatic plaque development.**

Dotted arrows – suppression.

Process intensity:
white – weak;
beige – average inflammatory;
pink – high inflammatory;

# Phase 5. Psoriasis.




Link to connected section in e-book 28

# Y-model. Interaction of local processes.

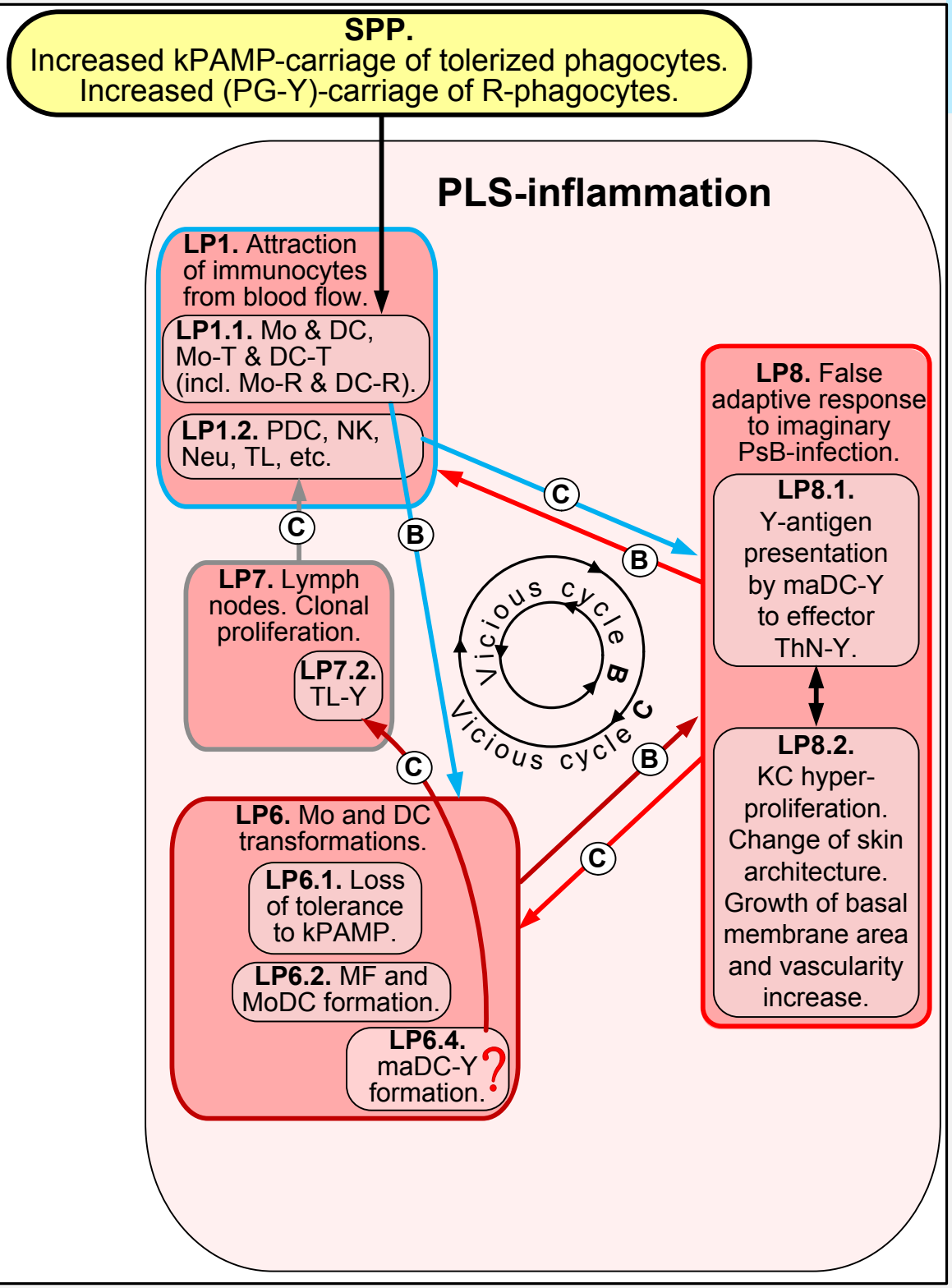
**Phases of psoriatic plaque development.**

Dotted arrows – suppression.

Process intensity: white – weak; beige – average inflammatory; pink – high inflammatory;

**Letters B and C - vicious cycles.**

# Phase 6. Psoriasis.




Phase starts when LP2, LP3 and LP5 end.

This phase is common for any LP2.

LP8 became self-sufficient. ?

Link to connected section in e-book

29

# Y-model. Interaction of local processes.

**Phases of psoriatic plaque development.**

Dotted arrows – suppression.

Process intensity: white – weak; beige – average inflammatory; pink – high inflammatory;

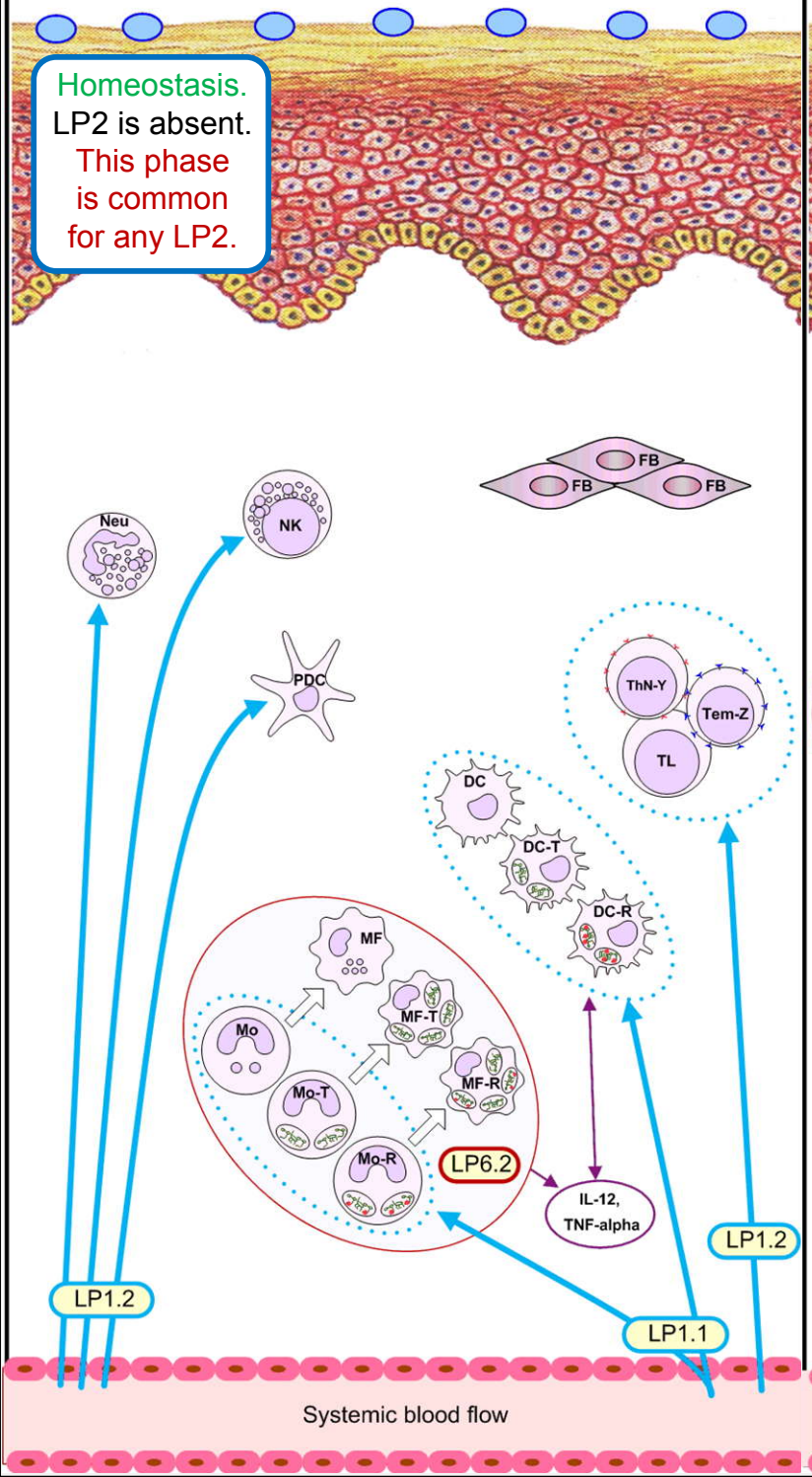
**Letters B and C - vicious cycles.**

# Psoriatic plaque development at LP2(IN). Open trauma of derma.

*Phases from 1 to 6: Slides 31-33 and 39.*

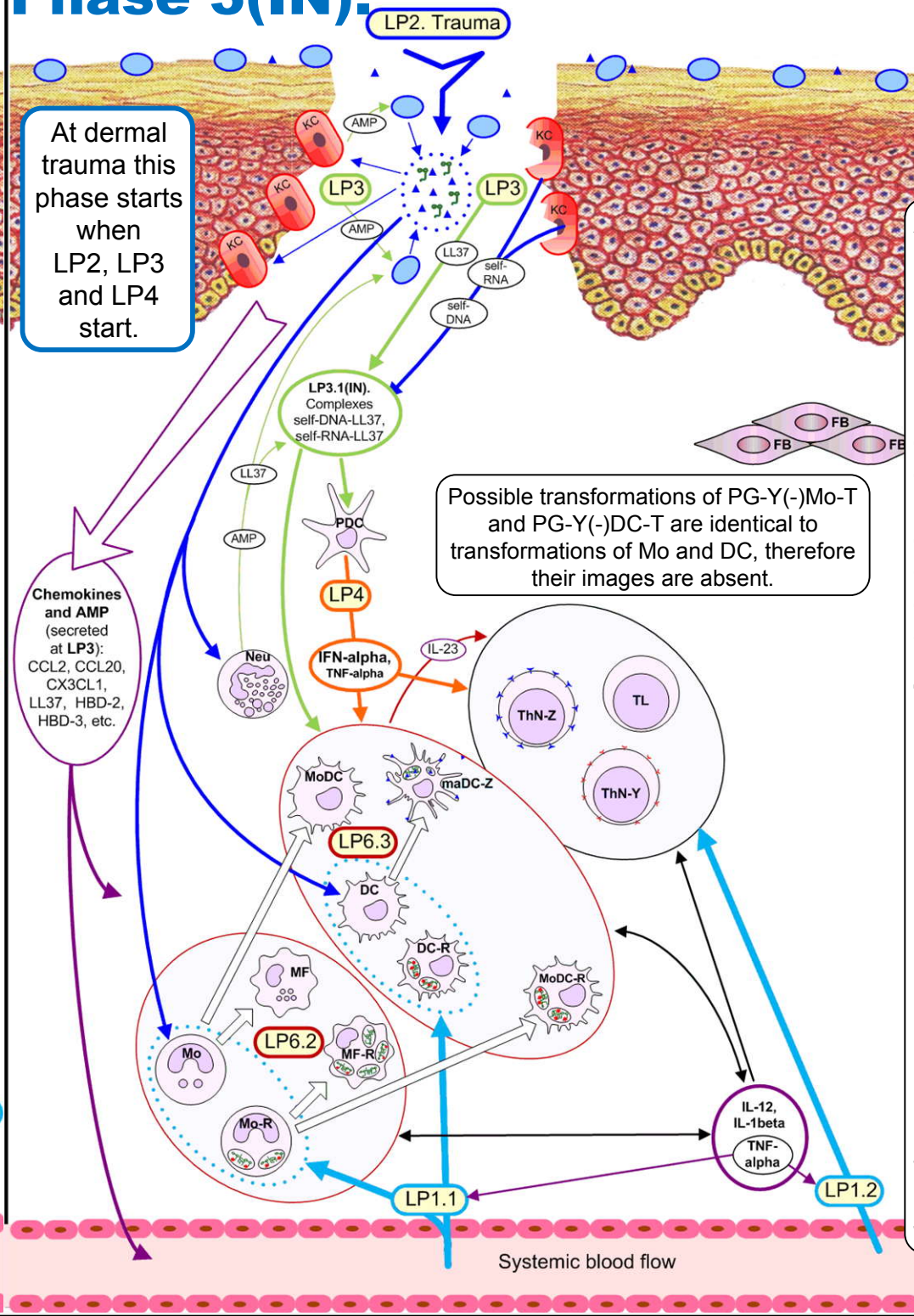
# Phase 1.

Homeostasis.
LP2 is absent.
This phase is common for any LP2.




# Phase 3(IN).

At dermal trauma this phase starts when LP2, LP3 and LP4 start.




Link to connected section in e-book

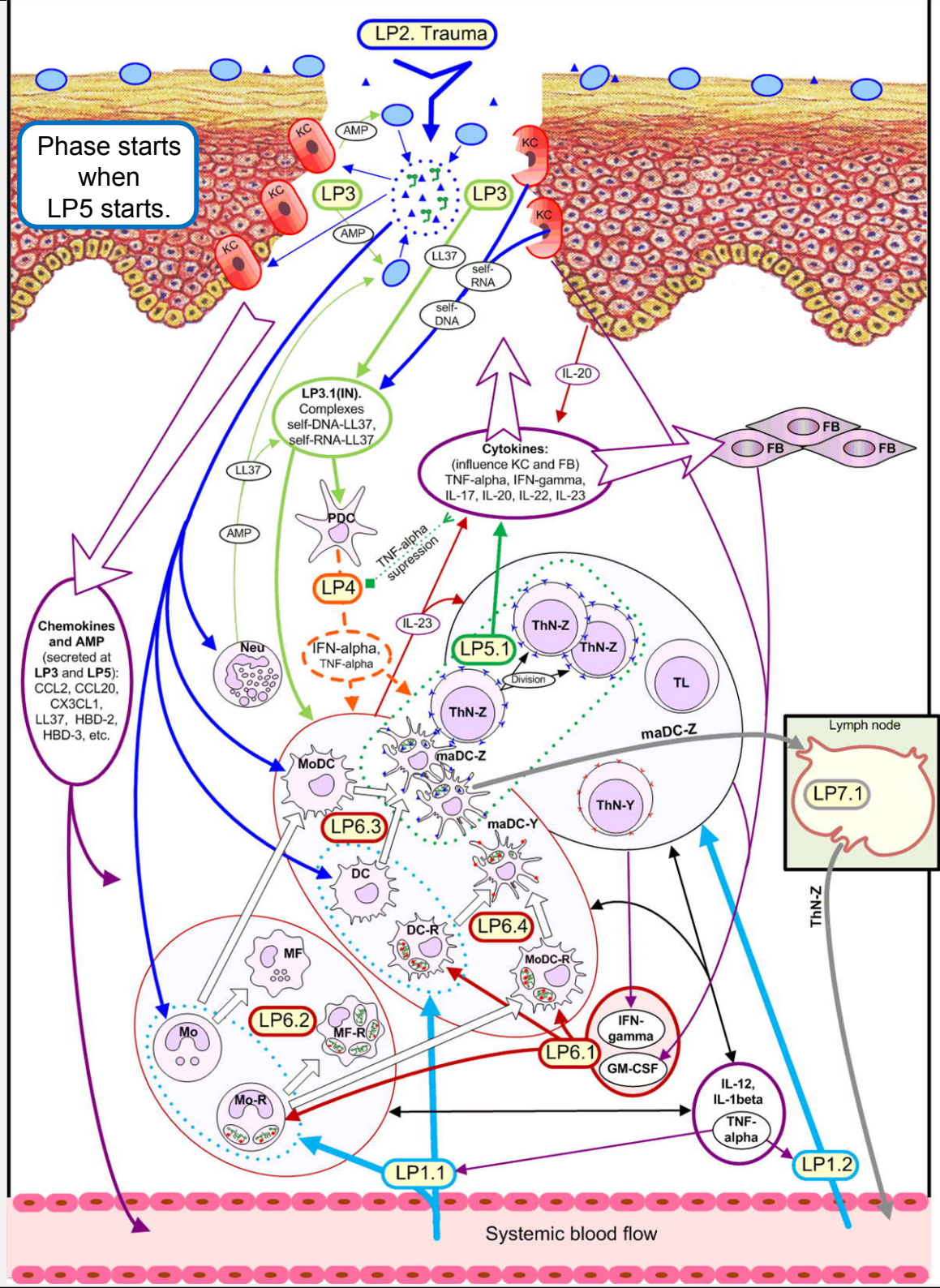
**AMP** = Anti-microbial proteins
**FB** = Fibroblasts
**KC** = Keratinocytes
**Neu** = Neutrophiles
**PDC** = Plasmacytoid dendritic cells
**TL** = any T-lymphocytes
**Tem-Z** = Z-specific effector memory TL
**ThN-Y** = Y-specific Th1, Th17 and Th22
**ThN-Z** = Z-specific Th1, Th17 and Th22
**Z** = Dominant antigen, presented through MHC class II for ThN-Z.

**Local processes:**
**LP1.1.** Attraction of all Mo and DC
**LP1.2.** Attraction of others immunocytes
**LP2(IN).** Open trauma of derma
**LP3.** Innate response after trauma
**LP4.** Trigger of adative response after trauma
**LP6.2.** MF and MoDC formation
**LP6.3.** maDC-Z formation

# Phase 4(IN).

Link to connected section in e-book






**AMP** = Anti-microbial proteins
**FB** = Fibroblasts
**KC** = Keratinocytes
**Neu** = Neutrophiles
**maDC-Y** = mature DC, derived from DC-R or MoDC-R and presenting Y-antigen
**maDC-Z** = mature DC, presenting Z-antigen
**PDC** = Plasmacytoid dendritic cells
**TL** = Any T-lymphocytes
**ThN-Y** = Y-specific Th1, Th17 and Th22
**ThN-Z** = Z-specific Th1, Th17 and Th22
**Z** = Dominant antigen, presented through MHC class II for ThN-Z.

**Local processes:**

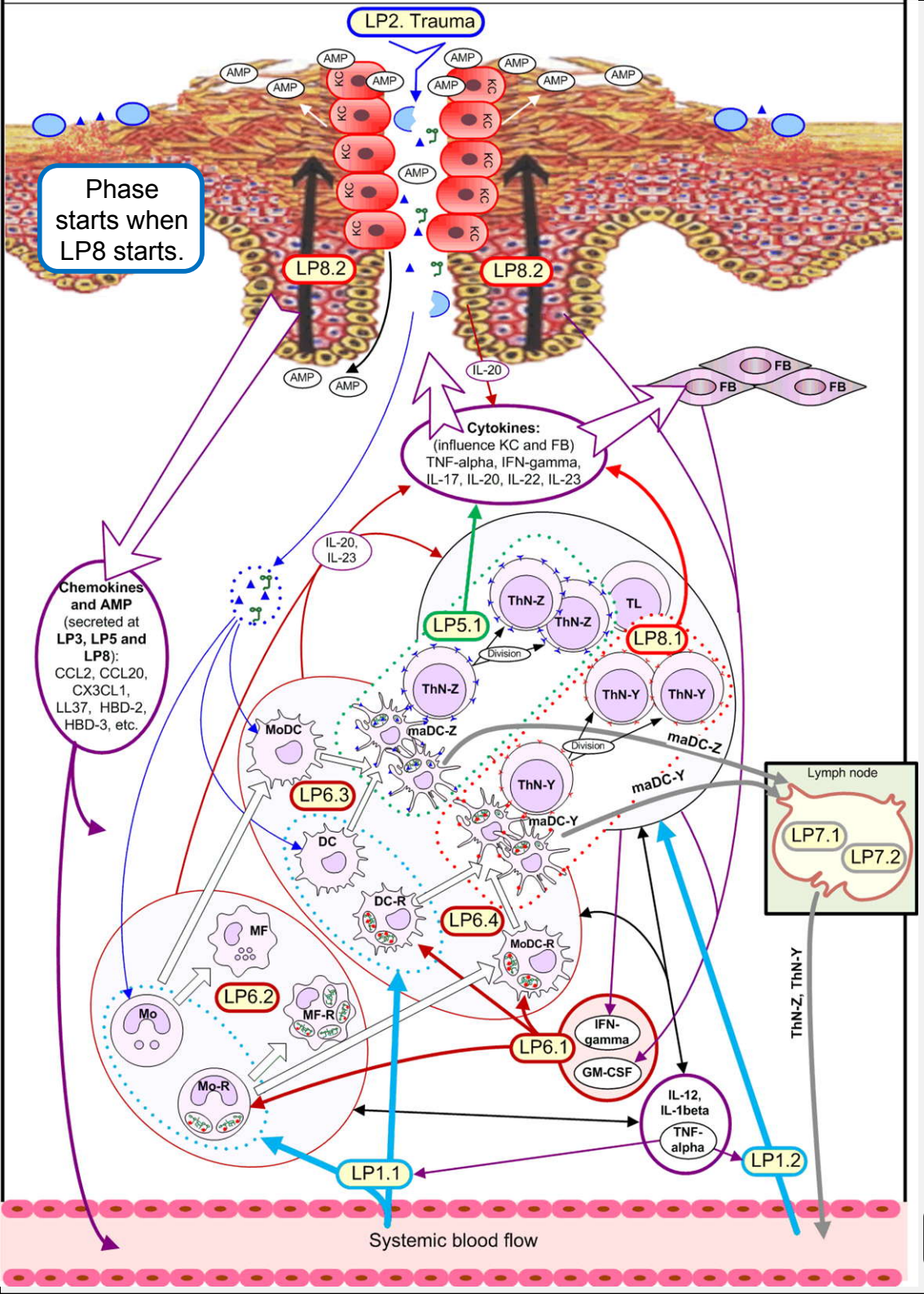
**LP1.1.** Attraction of all Mo and DC
**LP1.2.** Attraction of others immunocytes
**LP2(IN).** Open trauma of derma
**LP3.** Innate response after trauma
**LP3.1(IN).** Formation of self-DNA-LL37 and self-RNA-LL37 complexes
**LP4.** Trigger of adative response after trauma
**LP5.1.** Adaptive response after trauma
**LP6.1.** Loss tolerance to kPAMP
**LP6.2.** MF and MoDC formation
**LP6.3.** maDC-Z formation
**LP6.4.** maDC-Y formation
**LP7.1.** Clonal prolipheration of Tem-Z

Possible transformations of PG-Y(-)Mo-T and PG-Y(-)DC-T are identical to transformations of Mo and DC, therefore their images are absent.

# Phase 5(IN).

Link to connected section in e-book






**AMP** = Anti-microbial proteins
**FB** = Fibroblasts
**KC** = Keratinocytes
**maDC-Y** = mature DC, derived from DC-R or MoDC-R and presenting Y-antigen
**maDC-Z** = mature DC, presenting Z-antigen
**TL** = Any T-lymphocytes
**ThN-Y** = Y-specific Th1, Th17 and Th22
**ThN-Z** = Z-specific Th1, Th17 and Th22
**Z** = Dominant antigen, presented through MHC class II for ThN-Z.

**Local processes:**
**LP1.1.** Attraction of all Mo and DC
**LP1.2.** Attraction of others immunocytes
**LP2(IN).** Open trauma of derma
**LP3.** Innate response after trauma
**LP3.1(IN).** Formation of self-DNA-LL37 and self-RNA-LL37 complexes
**LP4.** Trigger of adative response after trauma
**LP5.1.** Adaptive response after trauma
**LP6.1.** Loss tolerance to kPAMP
**LP6.2.** MF and MoDC formation
**LP6.3.** maDC-Z formation
**LP6.4.** maDC-Y formation
**LP7.1.** Clonal prolipheration of Tem-Z
**LP7.2.** Clonal prolipheration of ThN-Y
**LP8.1.** Y-antigen presentation by maDC-Y to effector ThN-Y
**LP8.2.** KC hyperproliferation. Change of skin architecture. Growth of basal membrane area and vascularity increase.

Phase 6 on slide 39

Possible transformations of PG-Y(-)Mo-T and PG-Y(-)DC-T are identical to transformations of Mo and DC, therefore their images are absent.

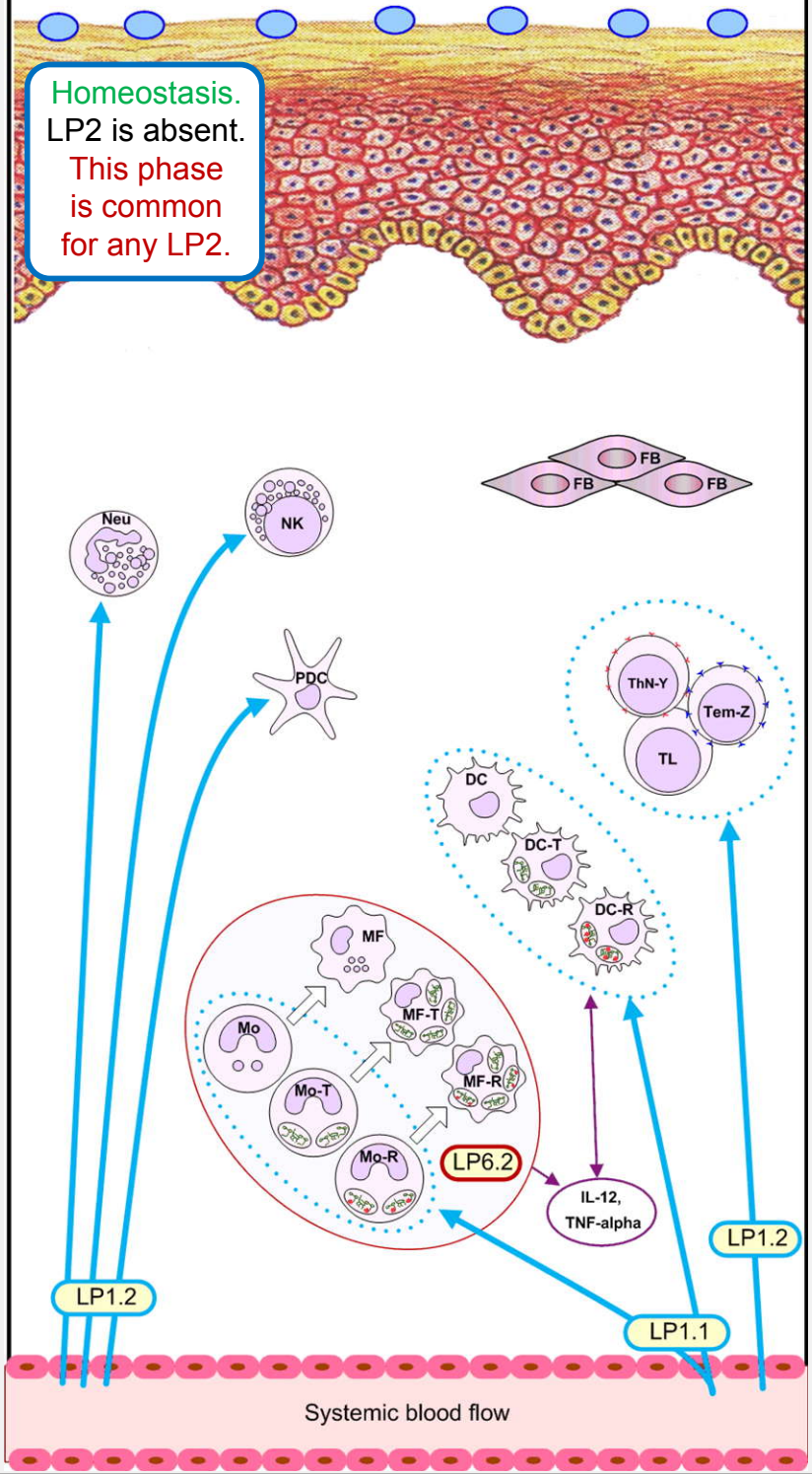
# Psoriatic plaque development at LP2(HPV). HPV-carriage of keratinocytes.

*Phases from 1 to 6: Slides 35-39.*

Link to connected section in e-book

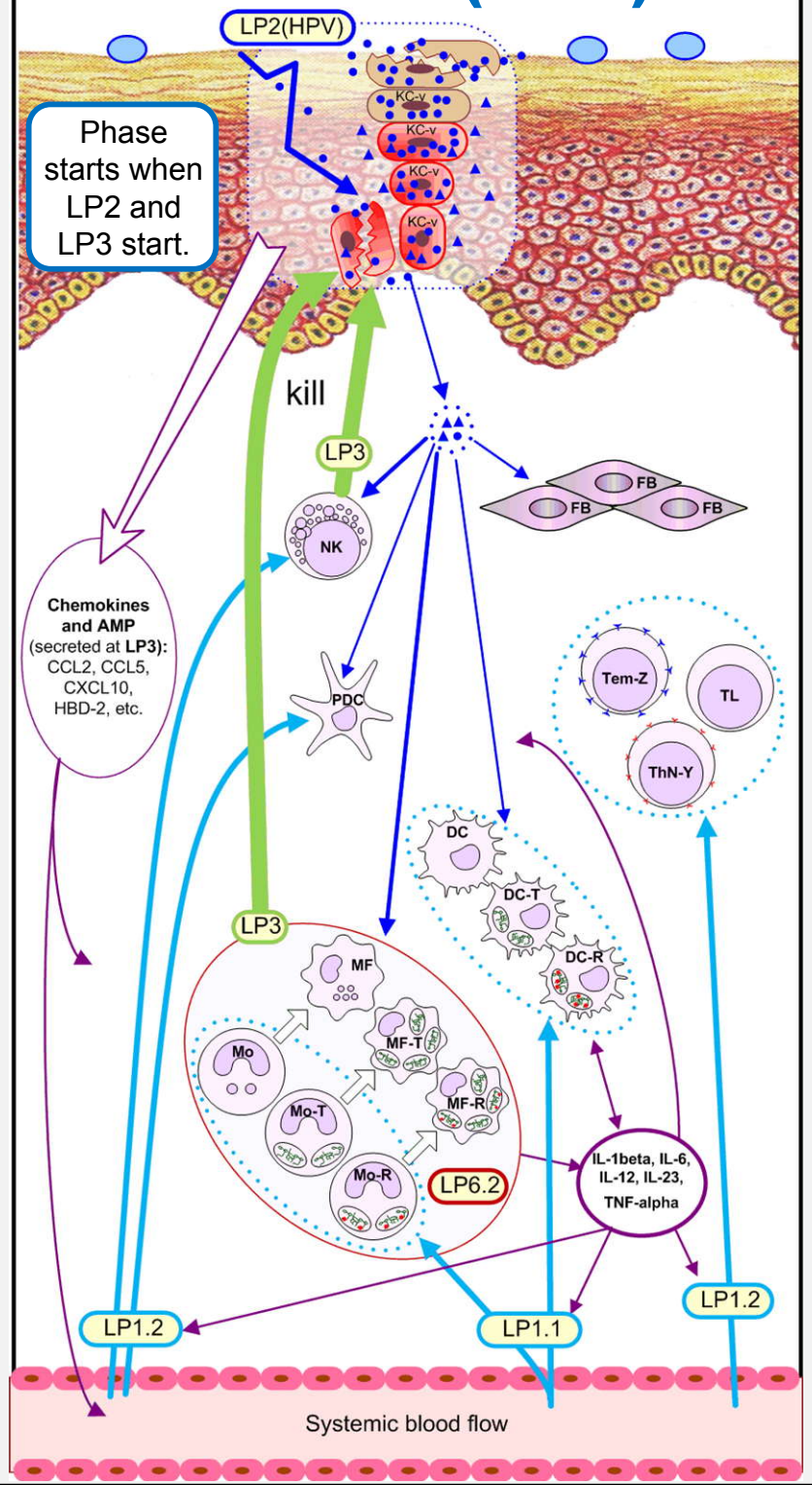

# Phase 1.

Homeostasis.
LP2 is absent.
This phase is common for any LP2.




# Phase 2(HPV).

Phase starts when LP2 and LP3 start.



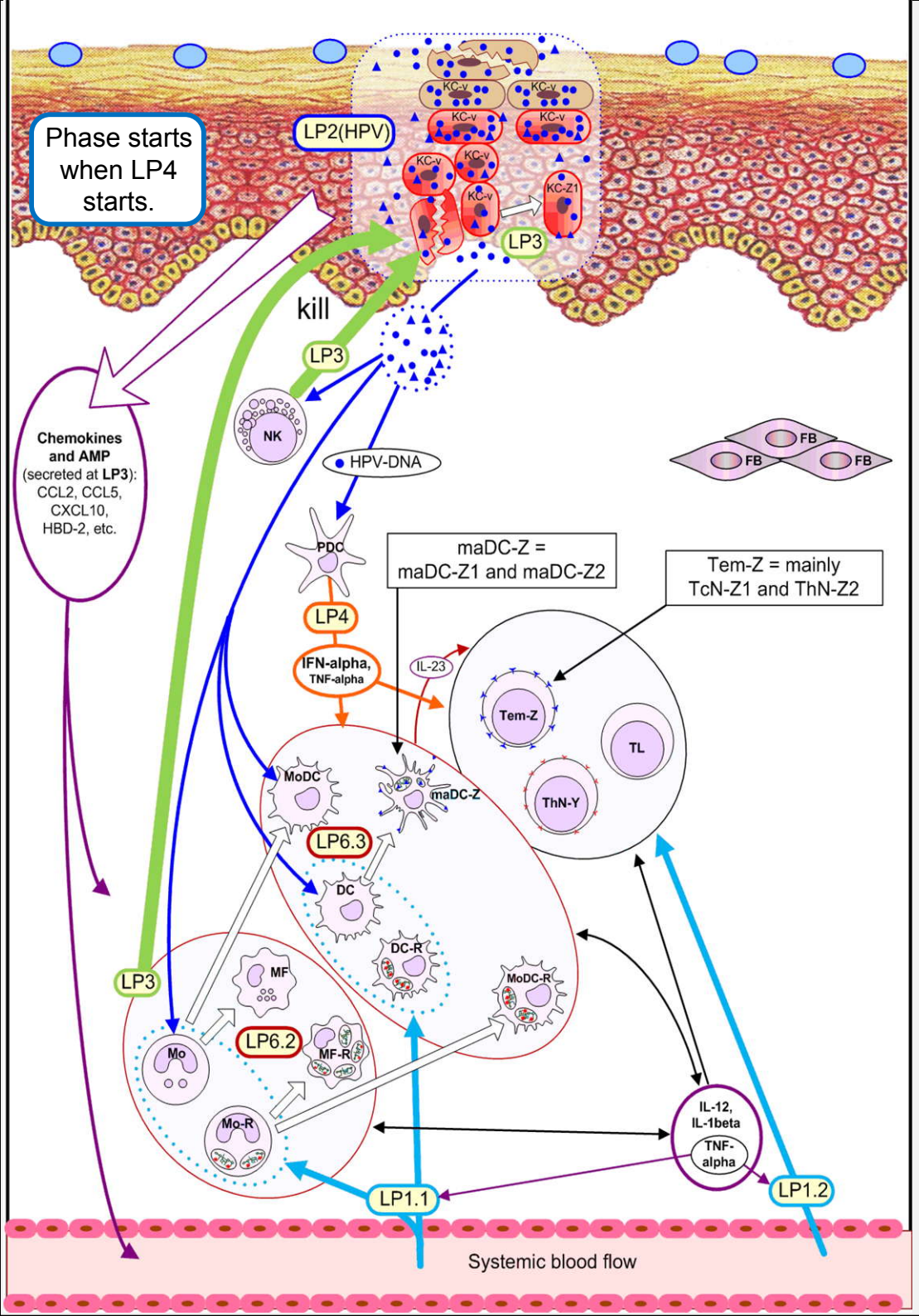

**AMP** = Anti-microbial proteins
**FB** = Fibroblasts
**KC** = Keratinocytes
**KC-v** = HPV-carring keratinocytes
**NK** = Natural killers
**PDC** = Plasmacytoid dendritic cells
**TL** = any T-lymphocytes
**Tem-Z** = Z-specific effector memory TL
**ThN-Y** = Y-specific Th1, Th17 and Th22

**Local processes:**
**LP1.1.** Attraction of all Mo and DC
**LP1.2.** Attraction of others immunocytes
**LP2(HPV).** HPV-carriage of keratinocytes
**LP3(HPV).** Innate response against HPV
**LP6.2.** MF and MoDC formation

# Phase 3(HPV).

Link to connected section in e-book






**AMP** = Anti-microbial proteins
**FB** = Fibroblasts
**KC** = Keratinocytes
**KC-v** = HPV-carring keratinocytes
**KC-Z1** = HPV-carring keratinocytes presenting Z1-antigen
**maDC-Z** = mature DC, presenting Z-antigen
**NK** = Natural killers
**PDC** = Plasmacytoid dendritic cells
**TL** = Any T-lymphocytes
**TcN-Z1** = Z1-specific TcN
**TcN** = Tc1, Tc17 and Tc22
**Tem-Z** = Z-specific effector memory TL
**ThN-Y** = Y-specific Th1, Th17 and Th22
**Z** = Z1 or Z2
**Z1** = Dominant antigen, presented through MHC class I for TcN-Z1.
**Z2** = Dominant antigen, presented through MHC class II for ThN-Z2.

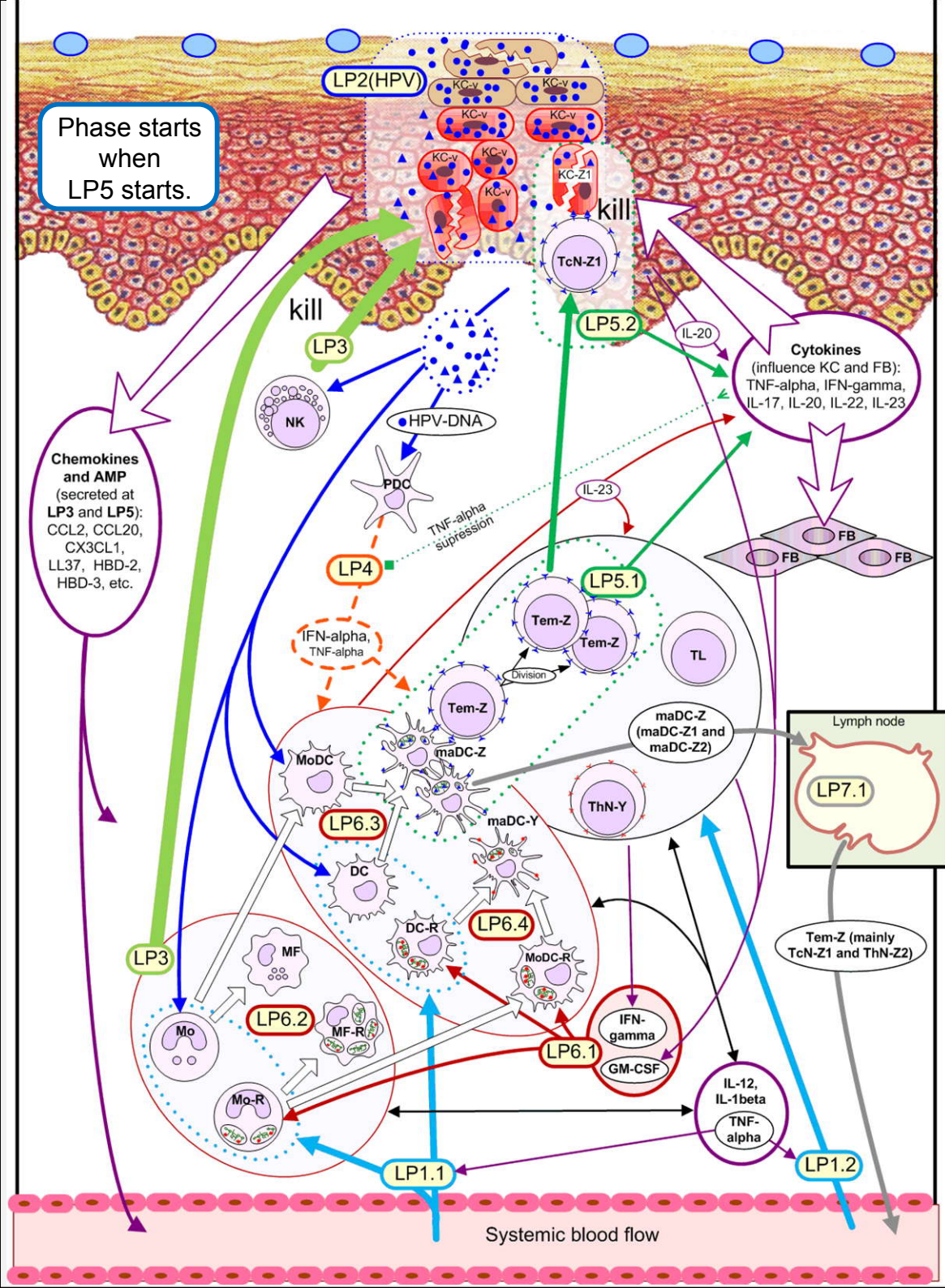
**Local processes:**
**LP1.1.** Attraction of all Mo and DC
**LP1.2.** Attraction of others immunocytes
**LP2(HPV).** HPV-carriage of keratinocytes
**LP3(HPV).** Innate response against HPV
**LP4(HPV).** Trigger of adative response against HPV
**LP6.2.** MF and MoDC formation
**LP6.3.** maDC-Z formation

Possible transformations of PG-Y(-)Mo-T and PG-Y(-)DC-T are identical to transformations of Mo and DC, therefore their images are absent.

# Phase 4(HPV).

Link to connected section in e-book






**AMP** = Anti-microbial proteins
**FB** = Fibroblasts
**KC** = Keratinocytes
**KC-v** = HPV-carring keratinocytes
**KC-Z1** = HPV-carring keratinocytes presenting Z1-antigen
**maDC-Y** = mature DC, derived from DC-R or MoDC-R and presenting Y-antigen
**maDC-Z** = mature DC, presenting Z-antigen
**NK** = Natural killers
**PDC** = Plasmacytoid dendritic cells
**TL** = Any T-lymphocytes
**TcN-Z1** = Z1-specific TcN
**TcN** = Tc1, Tc17 and Tc22
**Tem-Z** = Z-specific effector memory TL
**ThN-Y** = Y-specific Th1, Th17 and Th22
**Z** = Z1 or Z2
**Z1** = Dominant antigen, presented through MHC class I for TcN-Z1.
**Z2** = Dominant antigen, presented through MHC class II for ThN-Z2.

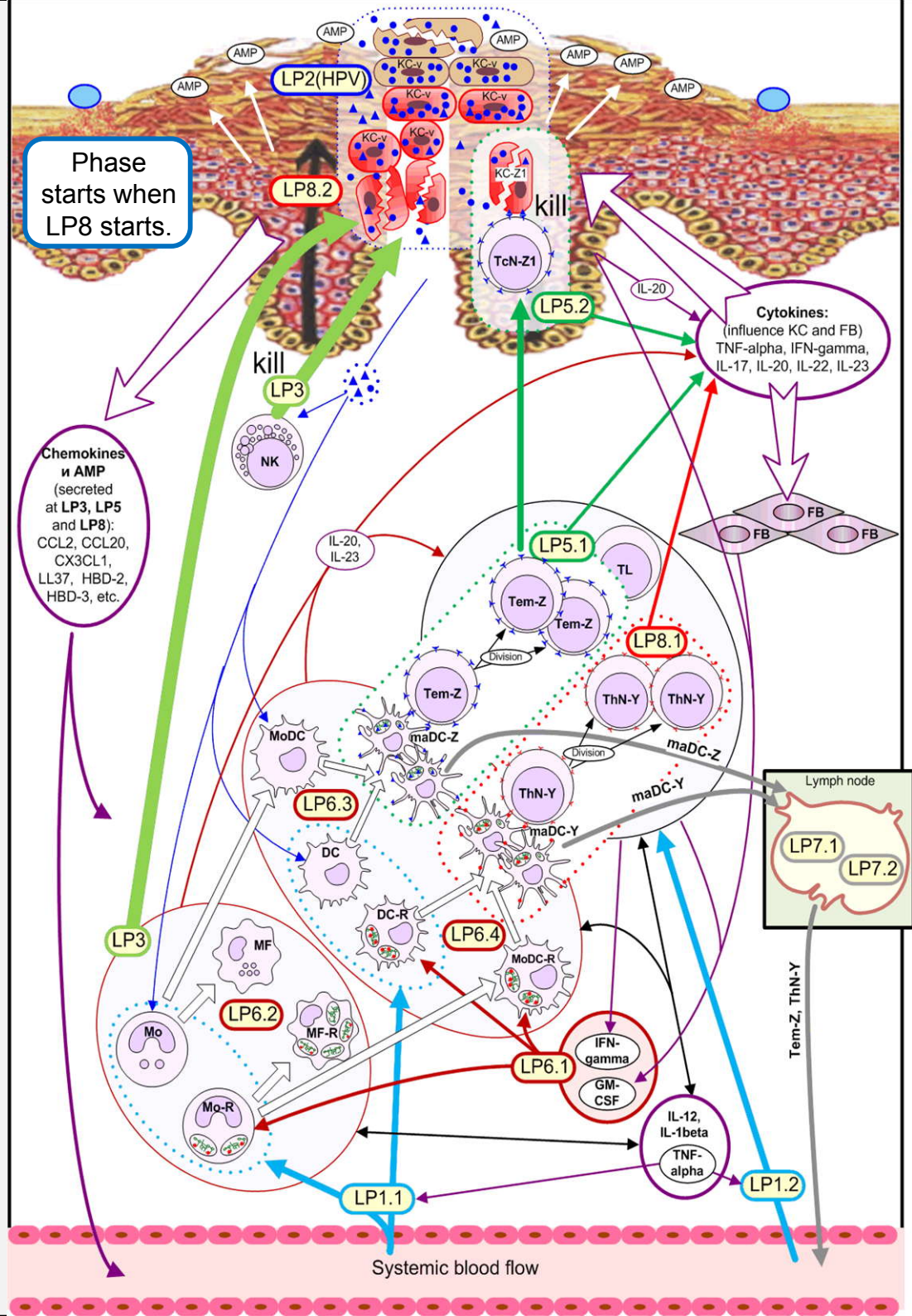
**Local processes:**
**LP1.1.** Attraction of all Mo and DC
**LP1.2.** Attraction of others immunocytes
**LP2(HPV).** HPV-carriage of keratinocytes
**LP3(HPV).** Innate response against HPV
**LP4(HPV).** Trigger of adative response against HPV
**LP5.1(HPV).** Adaptive response against HPV (derma)
**LP5.2(HPV).** Adaptive response against HPV (epidermis)
**LP6.1.** Loss tolerance to kPAMP
**LP6.2.** MF and MoDC formation
**LP6.3.** maDC-Z formation
**LP6.4.** maDC-Y formation
**LP7.1.** Clonal prolipheration of Tem-Z

Possible transformations of PG-Y(-)Mo-T and PG-Y(-)DC-T are identical to transformations of Mo and DC, therefore their images are absent.

# Phase 5(HPV).

Link to connected section in e-book






**AMP** = Anti-microbial proteins
**FB** = Fibroblasts
**KC** = Keratinocytes
**KC-v** = HPV-carring keratinocytes
**KC-Z1** = HPV-carring keratinocytes presenting Z1-antigen
**maDC-Y** = mature DC, derived from DC-R or MoDC-R and presenting Y-antigen
**maDC-Z** = mature DC, presenting Z-antigen
**NK** = Natural killers
**TL** = Any T-lymphocytes
**TcN-Z1** = Z1-specific TcN
**TcN** = Tc1, Tc17 and Tc22
**Tem-Z** = Z-specific effector memory TL
**ThN-Y** = Y-specific Th1, Th17 and Th22
**Z** = Z1 or Z2
**Z1** = Dominant antigen, presented through MHC class I for TcN-Z1.
**Z2** = Dominant antigen, presented through MHC class II for ThN-Z2.

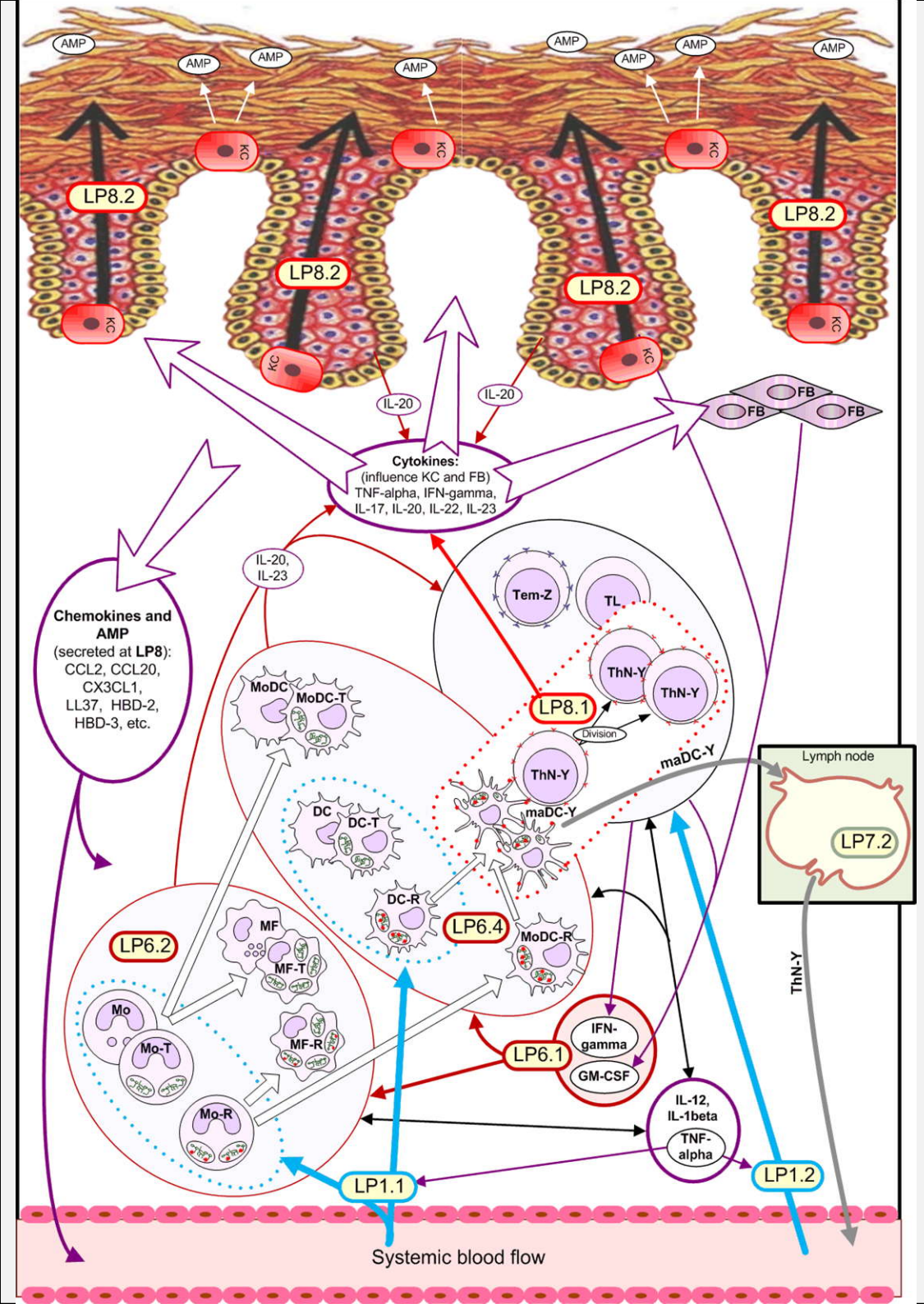
**Local processes:**
**LP1.1.** Attraction of all Mo and DC
**LP1.2.** Attraction of others immunocytes
**LP2(HPV).** HPV-carriage of keratinocytes
**LP3(HPV).** Innate response against HPV
**LP5.1(HPV).** Adaptive response against HPV (derma)
**LP5.2(HPV).** Adaptive response against HPV (epidermis)
**LP6.1.** Loss tolerance to kPAMP
**LP6.2.** MF and MoDC formation
**LP6.3.** maDC-Z formation
**LP6.4.** maDC-Y formation
**LP7.1.** Clonal prolipheration of Tem-Z
**LP7.2.** Clonal prolipheration of ThN-Y
**LP8.1.** Y-antigen presentation by maDC-Y to effector ThN-Y
**LP8.2.** KC hyperproliferation. Change of skin architecture. Growth of basal membrane area and vascularity increase.

Possible transformations of PG-Y(-)Mo-T and PG-Y(-)DC-T are identical to transformations of Mo and DC, therefore their images are absent.

# Phase 6.

Link to connected section in e-book






**AMP** = Anti-microbial proteins
**FB** = Fibroblasts
**KC** = Keratinocytes
**maDC-Y** = mature DC, derived from DC-R or MoDC-R and presenting Y-antigen
**TL** = any T-lymphocytes
**Tem-Z** = Z-specific effector memory TL
**ThN-Y** = Y-specific Th1, Th17 and Th22

**Local processes:**
**LP1.1.** Attraction of all Mo and DC
**LP1.2.** Attraction of others immunocytes
**LP6.1.** Loss tolerance
to kPAMP
**LP6.2.** MF and MoDC formation
**LP6.4.** Transformation
DC-R and MoDC-R in maDC-Y
**LP7.2.** Clonal prolipheration of ThN-Y
**LP8.1.** Y-antigen presentation by maDC-Y to effector ThN-Y
**LP8.2.** KC hyperproliferation. Change of skin architecture. Growth of basal membrane area and vascularity increase.

Phase starts when LP2, LP3 and LP5 end.

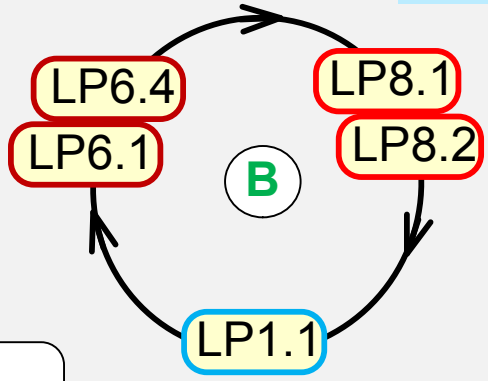
This phase is common for any LP2.

LP8 became self-sufficient. ?

# Phase 6. Vicious cycle B (for DC-R)



Link to connected section in e-book




To and from epidermis

**Cytokines:**
(influence KC and FB)
TNF-alpha, IFN-gamma, IL-17, IL-20, IL-22, IL-23

IL-20

FB

**Chemokines and AMP**
(secreted at **LP8**):
CCL2, CCL20, CX3CL1, LL37, HBD-2, HBD-3, etc.

IL-20, IL-23

GM-CSF

LP8.1

ThN-Y

ThN-Y

Division

maDC-Y

ThN-Y

DC-R

?

LP6.4

The severity of plaque is defined by intensity of Y-antigen income into derma (inside Mo-R and DC-R).

LP6.1

IFN-gamma

GM-CSF

IL-12, IL-1beta

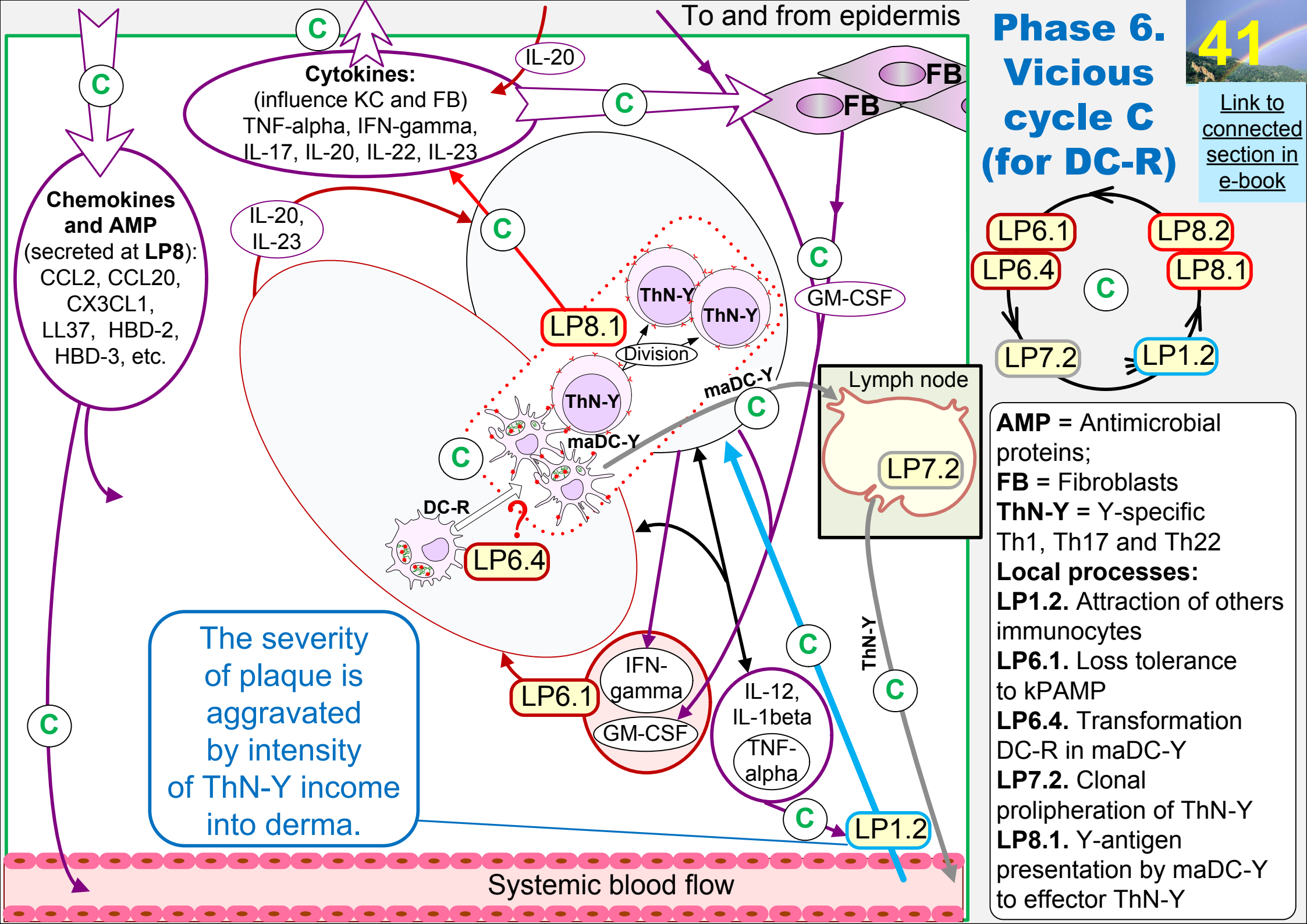
TNF-alpha

LP1.1

Systemic blood flow

**AMP** = Antimicrobial proteins
**FB** = Fibroblasts
**KC** = Keratinocytes
**ThN-Y** = Y-specific Th1, Th17 and Th22

**Local processes:**
**LP1.1.** Attraction of all Mo and DC
**LP6.1.** Loss tolerance to kPAMP
**LP6.4.** Transformation DC-R in maDC-Y
**LP8.1.** Y-antigen presentation by maDC-Y to effector ThN-Y
**LP8.2.** KC hyper-proliferation. Change of skin architecture. Growth of basal membrane area and vascularity increase.

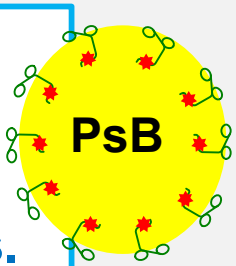

To and from epidermis
Phase 6. Vicious cycle C (for DC-R)
41
Link to connected section in e-book
C
Cytokines:
(influence KC and FB)
TNF-alpha, IFN-gamma,
IL-17, IL-20, IL-22, IL-23
IL-20
FB
FB
Chemokines and AMP
(secreted at LP8):
CCL2, CCL20,
CX3CL1,
LL37, HBD-2,
HBD-3, etc.
IL-20,
IL-23
GM-CSF
LP8.1
ThN-Y
ThN-Y
Division
ThN-Y
maDC-Y
maDC-Y
DC-R
?
LP6.4
Lymph node
LP7.2
LP6.1
IFN-gamma
GM-CSF
IL-12,
IL-1beta
TNF-alpha
ThN-Y
LP1.2
The severity of plaque is aggravated by intensity of ThN-Y income into derma.
Systemic blood flow
LP6.1
LP8.2
LP6.4
LP8.1
C
LP7.2
LP1.2
AMP = Antimicrobial proteins;
FB = Fibroblasts
ThN-Y = Y-specific Th1, Th17 and Th22
Local processes:
LP1.2. Attraction of others immunocytes
LP6.1. Loss tolerance to kPAMP
LP6.4. Transformation DC-R in maDC-Y
LP7.2. Clonal prolipheration of ThN-Y
LP8.1. Y-antigen presentation by maDC-Y to effector ThN-Y

# ? SPP. Hypotheses. ?

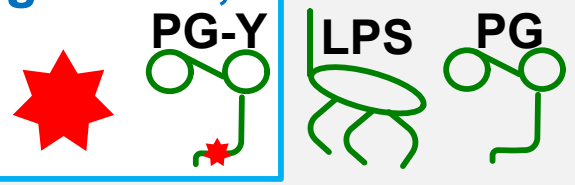
Link to connected section in e-book



**H1** SPP main reasons are small intestine colonization by Gram+ psoriagenic PsB and Gram(-) TLR4-active bacteria and its hyperpermeability for bacterial products. PsB are E.faecalis, Str.pyogenes, Str.agalactiae, VGS and some others.




**H2** PsB possess PG-Y - peptidoglycan with interpeptide bridges IB-Y, i.e. L-Ala(2-3) and-or L-Ala-L-Ser. Y-antigen is part(s) of interpeptide bridge IB-Y.



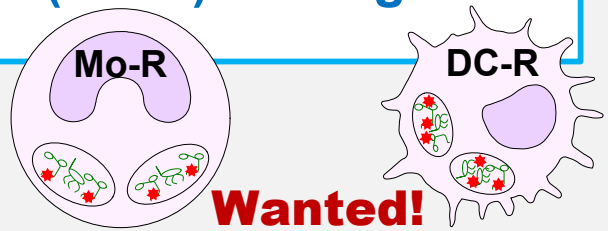

**H3** PAMP-nemia and (PG-Y)-nemia are main processes. kPAMP are LPS and PG.

**H4** Growth of tolerized fractions Mo-T and DC-T under chronic kPAMP-load. Their increased kPAMP-carriage. Fractions are formed as a result of long-term stay in blood flow.


**H5** Chemostatuses of tolerized Mo-T and DC-T are similar to nonactivated ones.

**H6** Growth of subfractions Mo-R and DC-R in blood under chronic kPAMP-load and (PG-Y)-load. SPP severity is proportional to their total (PG-Y)-carriage.

**H7** SPP is a weak CARS (compensatory anti-inflammatory response syndrome).



# ? Local processes. Hypotheses. ?

Link to connected section in e-book



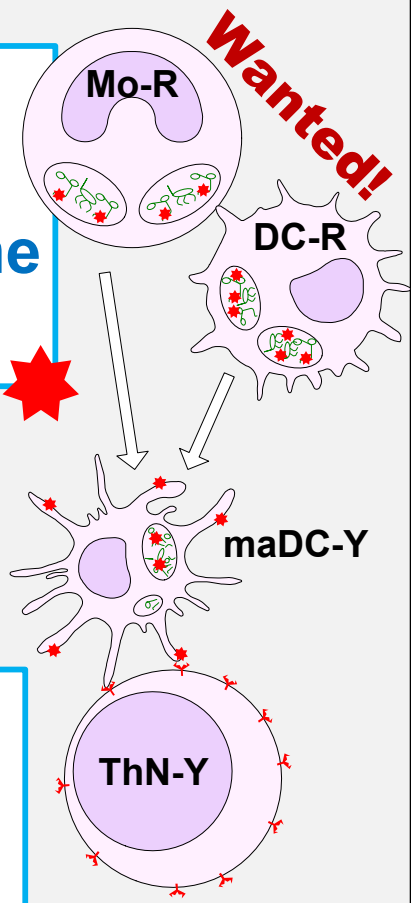
**H8** Koebnerization is complex: LP2 – initiating and aggravating process; LP3 – innate response against LP2; LP4 – trigger of adaptive response; LP5 – adaptive response against LP2. LP5 is necessary for any plaque initialization.

**H9** HPV-carriage of keratinocytes is possible LP2.

**H10** Attraction of Mo-R and DC-R into derma from blood flow is a necessary vicious cycle link. Existence and severity of any plaque is defined by intensity of income into derma of Y-antigen brought by Mo-R and DC-R.

**H11** Loss of tolerance DC-R and Mo-R and their subsequent transformation in maDC-Y are necessary vicious cycle links.

**H12** Psoriatic inflammation (incl. KC hyperproliferation) is a reaction of SIS (skin immune system) to an imaginary PsB-infection. SIS defines this false target, based on Y-antigen presentation.



# Hypotheses that need to check first

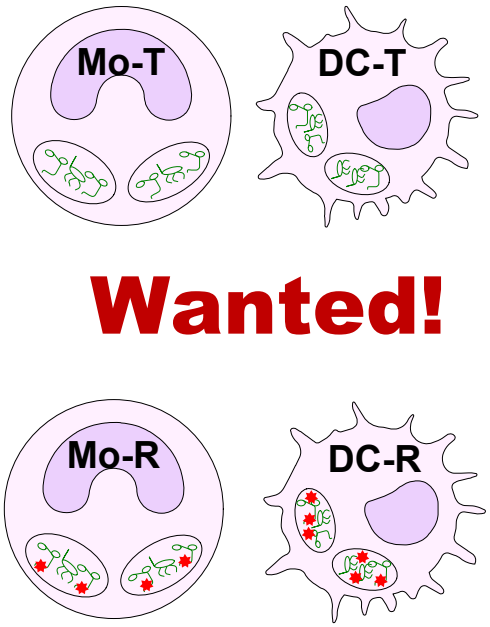
Link to connected section in e-book



**H4** Growth of tolerized fractions blood Mo-T and DC-T under chronic kPAMP-load. Their increased kPAMP-carriage. Fractions is formed from long-term stay blood Mo and DC.

**H5** Chemostatuses of tolerized Mo-T and DC-T are similar to nonactivated ones.

**H6** Growth of subfractions blood Mo-R and DC-R under chronic kPAMP-load and (PG-Y)-load. SPP severity is proportional to their total (PG-Y)-carriage.

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|---|---|
| Offence: | Human body damages |
| Time: | During and after damages made by others |
| Offence area: | Skin and joints |
| Nicknames: | Mo-T, DC-T (incl. Mo-R, DC-R) |
| Residence area: | Blood flow of psoriatic persons |
| Special signs: | Tolerized; kPAMP-carriers; Raised level of intracellular protein IRAK-M; (PG-Y)-carriers (Mo-R, DC-R only); |

**If you can help to find these phagocytes call ~~police~~ IFPA!**