APPLICATION ON INFLAMMATION

INFLAMMATION: DEFENCE AND REPAIR

Inflammation = protective, defense response to exogenous and endogenous stimuli

Inflammation = adaptive response that is triggered by noxious stimuli and conditions, such as infection and tissue injury

The general physiological role of inflammation is to restore tissue homeostasis

Regardless of the cause, inflammation presumably evolved as an adaptive response for restoring homeostasis

INFLAMMATION AND REPAIR

Inflammation: ACUTE and CHRONIC

Feature	Acute	Chronic
Onset	Fast: minutes or hours	Slow: days
Cellular infiltrate	Mainly neutrophils	Monocytes/macrophages and lymphocytes
Tissue injury, fibrosis	Usually mild and self-limited	May be severe and progressive
Local and systemic signs	Prominent	Less

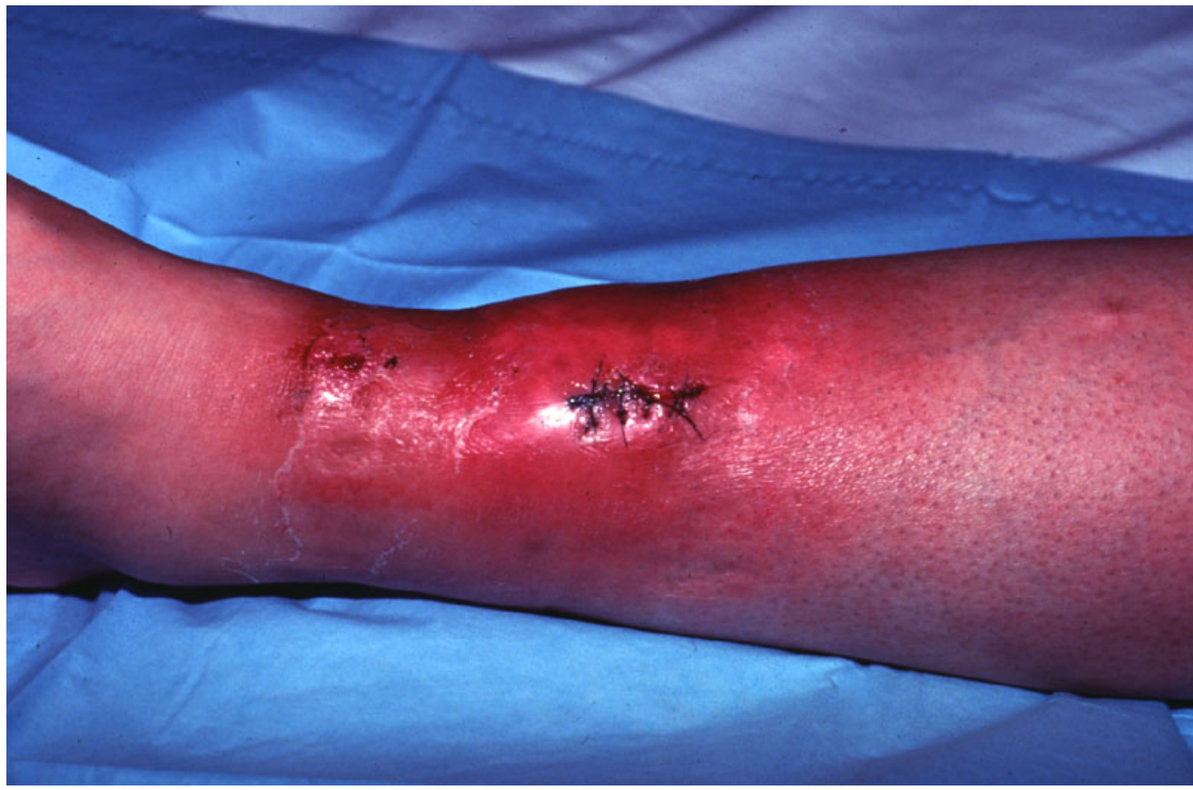
ACUTE INFLAMMATION

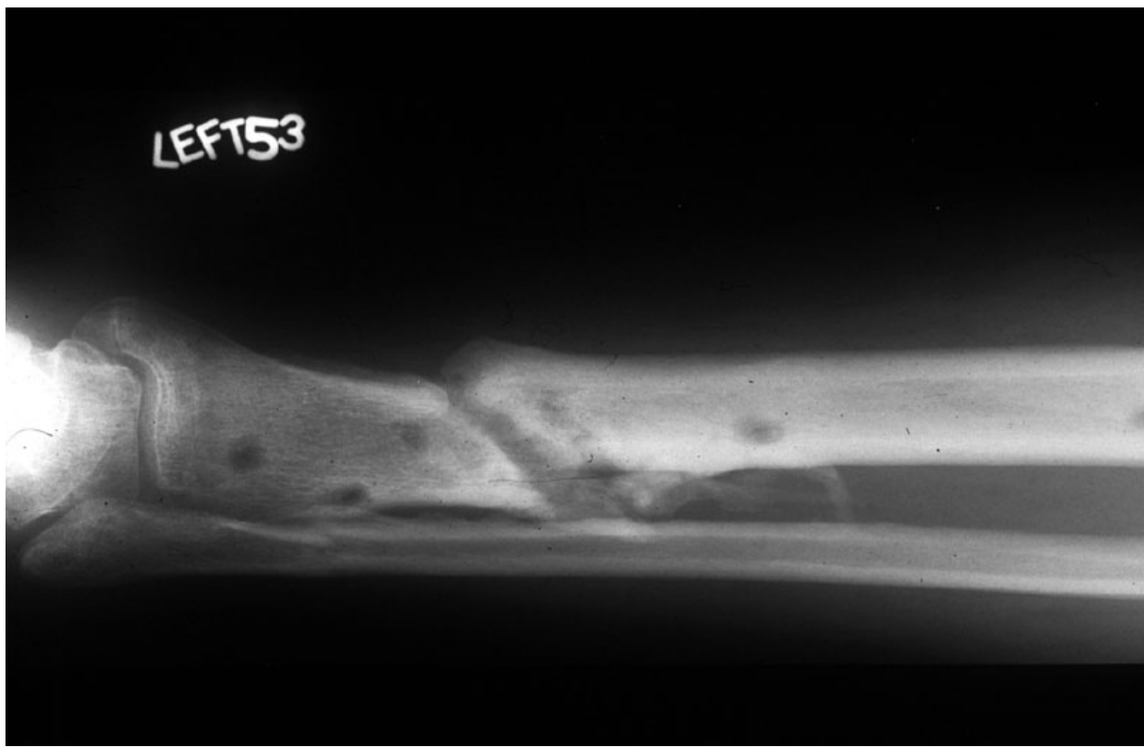
Has three major components:

(1) dilatation of small vessels, leading to an increase in blood flow,

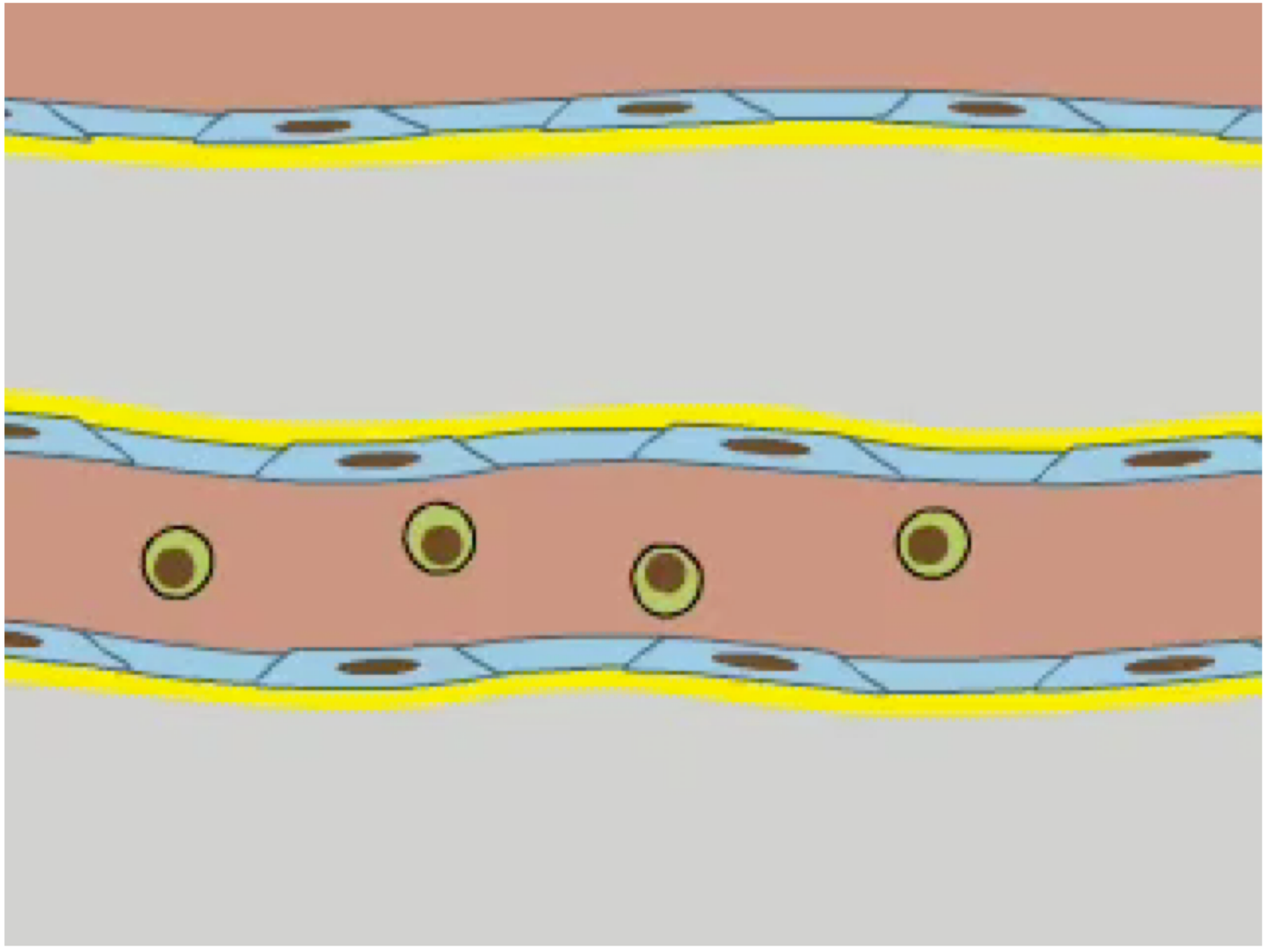
(2) increased permeability of the microvasculature, enabling plasma proteins and leukocytes to leave the circulation,

(3) emigration of the leukocytes from the microcirculation, their accumulation in the site of injury, and their activation to eliminate the offending agent

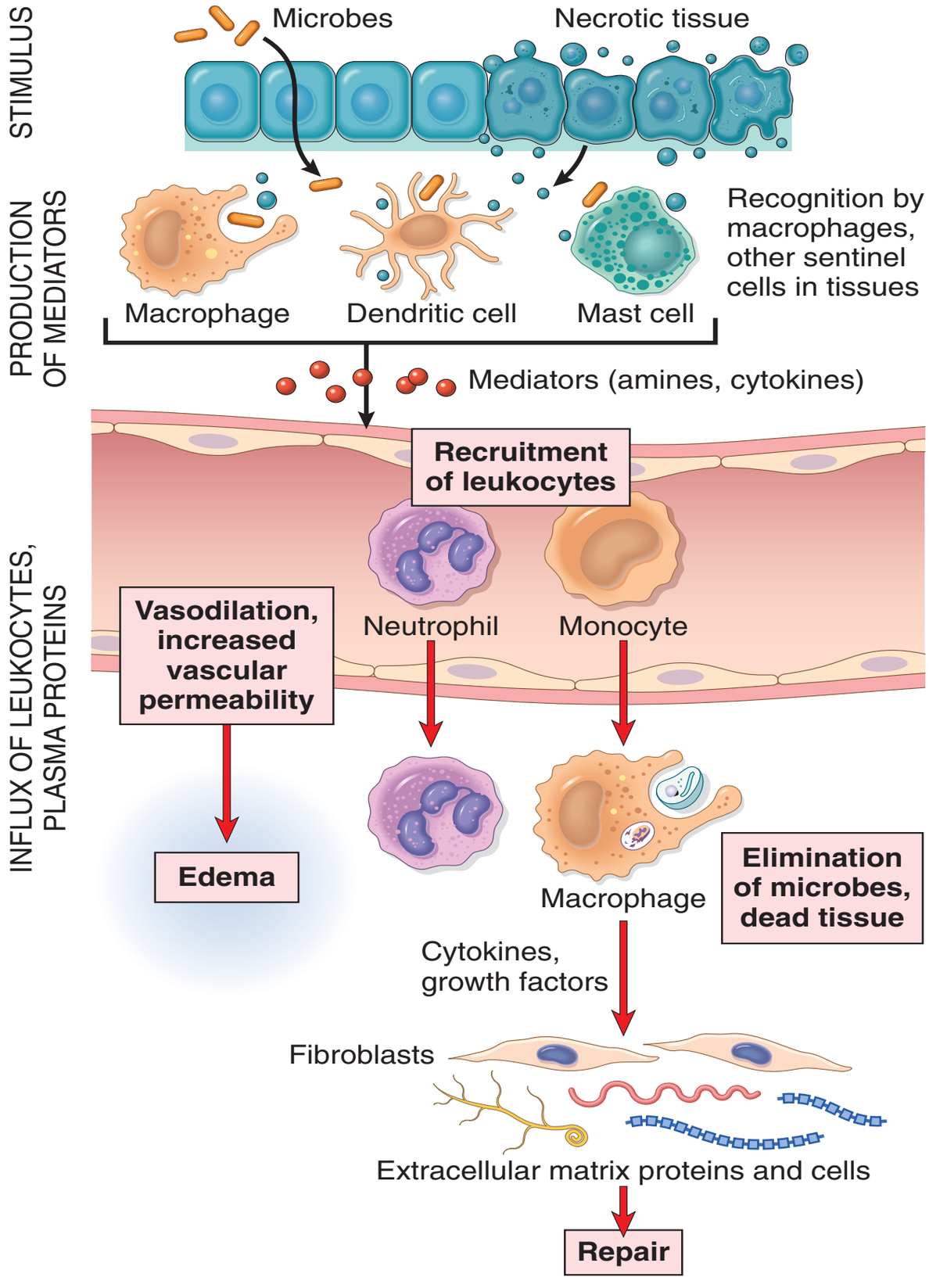




CELLULAR PHENOMENA:LEUKOCYTE MIGRATION



Sequence of events in an inflammatory reaction



Neutrophils and macrophages: innate cells of the acute inflammatory responses

	Neutrophils	Macrophages
Origin	HSCs in bone marrow	• HSCs in bone marrow (in inflammatory reactions) • Many tissue-resident macrophages: stem cells in yolk sac or fetal liver (early in development)
Life span in tissues	1–2 days	Inflammatory macrophages: days or weeks Tissue-resident macrophages: years
Responses to activating stimuli	Rapid, short-lived, mostly degranulation and enzymatic activity	More prolonged, slower, often dependent on new gene transcription
• Reactive oxygen species	Rapidly induced by assembly of phagocyte oxidase (respiratory burst)	Less prominent
• Nitric oxide	Low levels or none	Induced following transcriptional activation of iNOS
• Degranulation	Major response; induced by cytoskeletal rearrangement	Not prominent
• Cytokine production	Low levels or none	Major functional activity, requires transcriptional activation of cytokine genes
• NET formation	Rapidly induced, by extrusion of nuclear contents	No
• Secretion of lysosomal enzymes	Prominent	Less

ACUTE INFLAMMATION:

MEDIATORS OF INFLAMMATION

1. DERIVED FROM SOLUBLE POLYMOLECULAR SYSTEMS

- **COMPLEMENT SYSTEM**
- **KININ SYSTEM**
- **COAGULATION-FIBRINOLYTIC SYSTEM**

2. CELL-DERIVED:

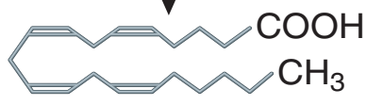
- PREFORMED: Histamine
Serotonine
Granule enzymes and other molecules

- NEWLY SYNTHESIZED: Prostaglandine
Leukotriens
PAF (platelet activating factor)
ROS, NO
Cytokines (after hours)

Aracidonic acid metabolites

Cell membrane phospholipids

Steroids ⊣ **Phospholipases**



ARACHIDONIC ACID

Other lipoxygenases → HPETEs → HETEs

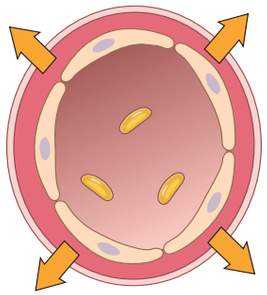
COX-1 and COX-2 inhibitors, aspirin, indomethacin ⊣ **Cyclooxygenase**

Lipoxygenase inhibitors ⊣ **5-Lipoxygenase**

Prostaglandin G_2 (PGG_2)

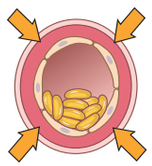
Prostaglandin H_2 (PGH_2)

Prostacyclin PGI_2



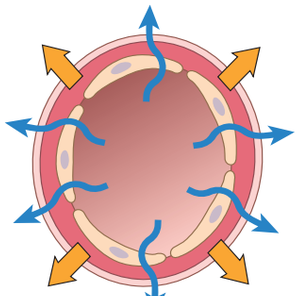
Causes vasodilation, inhibits platelet aggregation

Thromboxane A_2 TXA_2



Causes vasoconstriction, promotes platelet aggregation

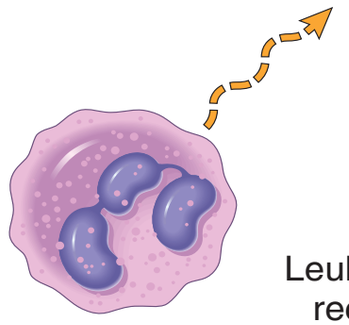
PGD_2 PGE_2



Causes vasodilation, increased vascular permeability

5-HPETE → **5-HETE**

Chemotaxis



Leukotriene receptor antagonists

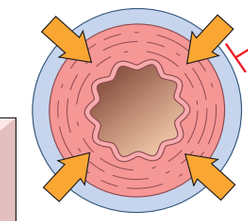
Leukotriene A_4 (LTA_4) → **Leukotriene B_4**

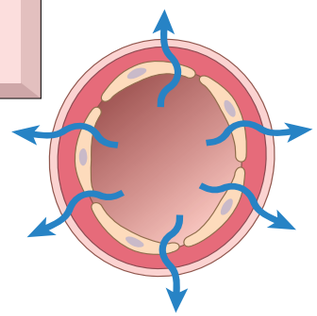
Leukotriene C_4 (LTC_4)

Leukotriene D_4 (LTD_4)

Leukotriene E_4 (LTE_4)

Bronchospasm
Increased vascular permeability

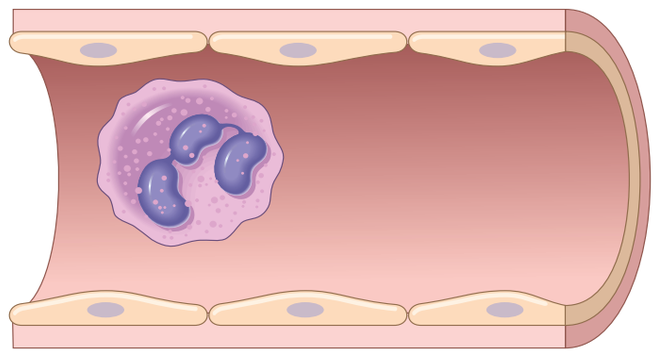




12-Lipoxygenase

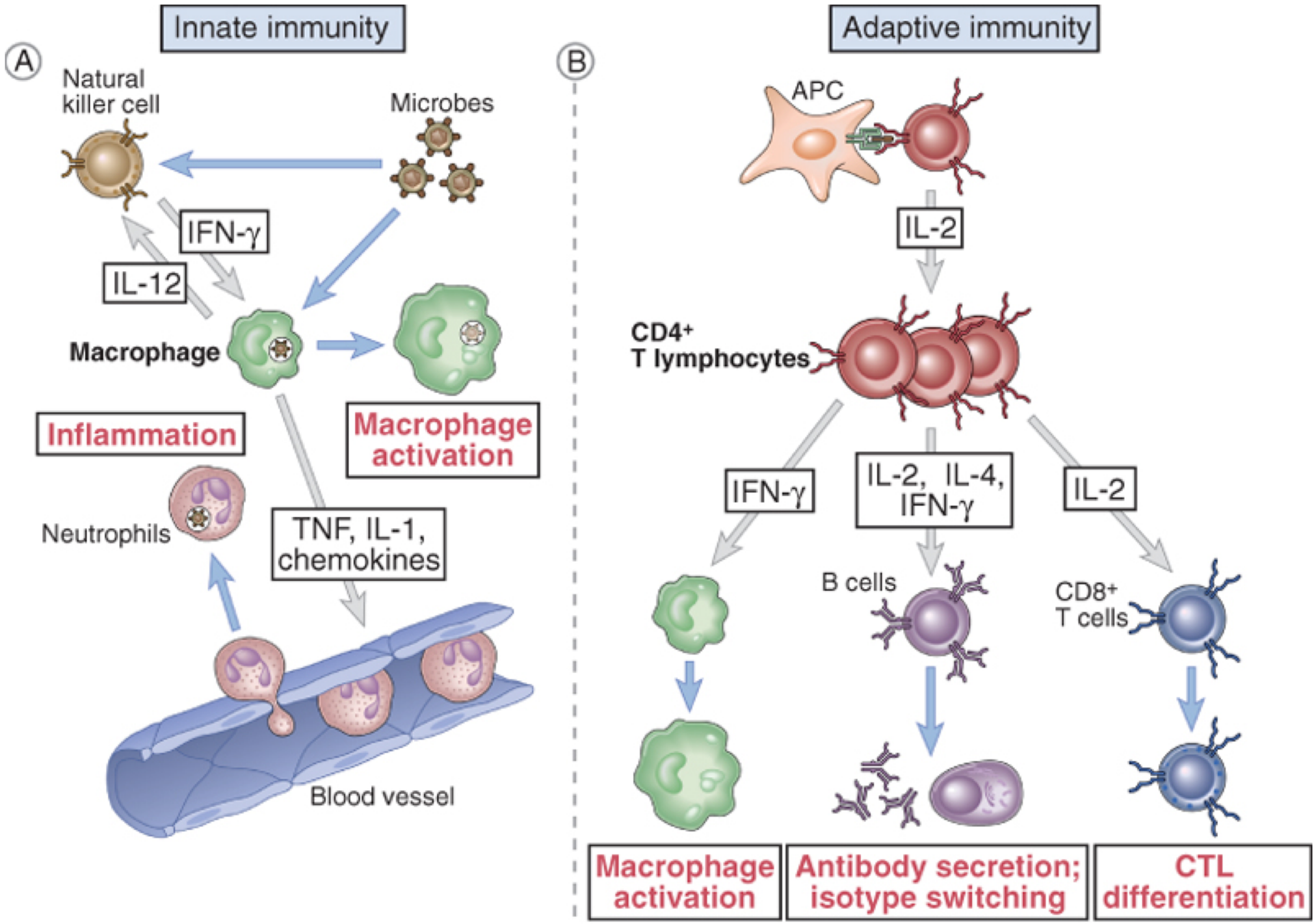
Lipoxin A_4 (LXA_4)
Lipoxin B_4 (LXB_4)

Inhibition of inflammation

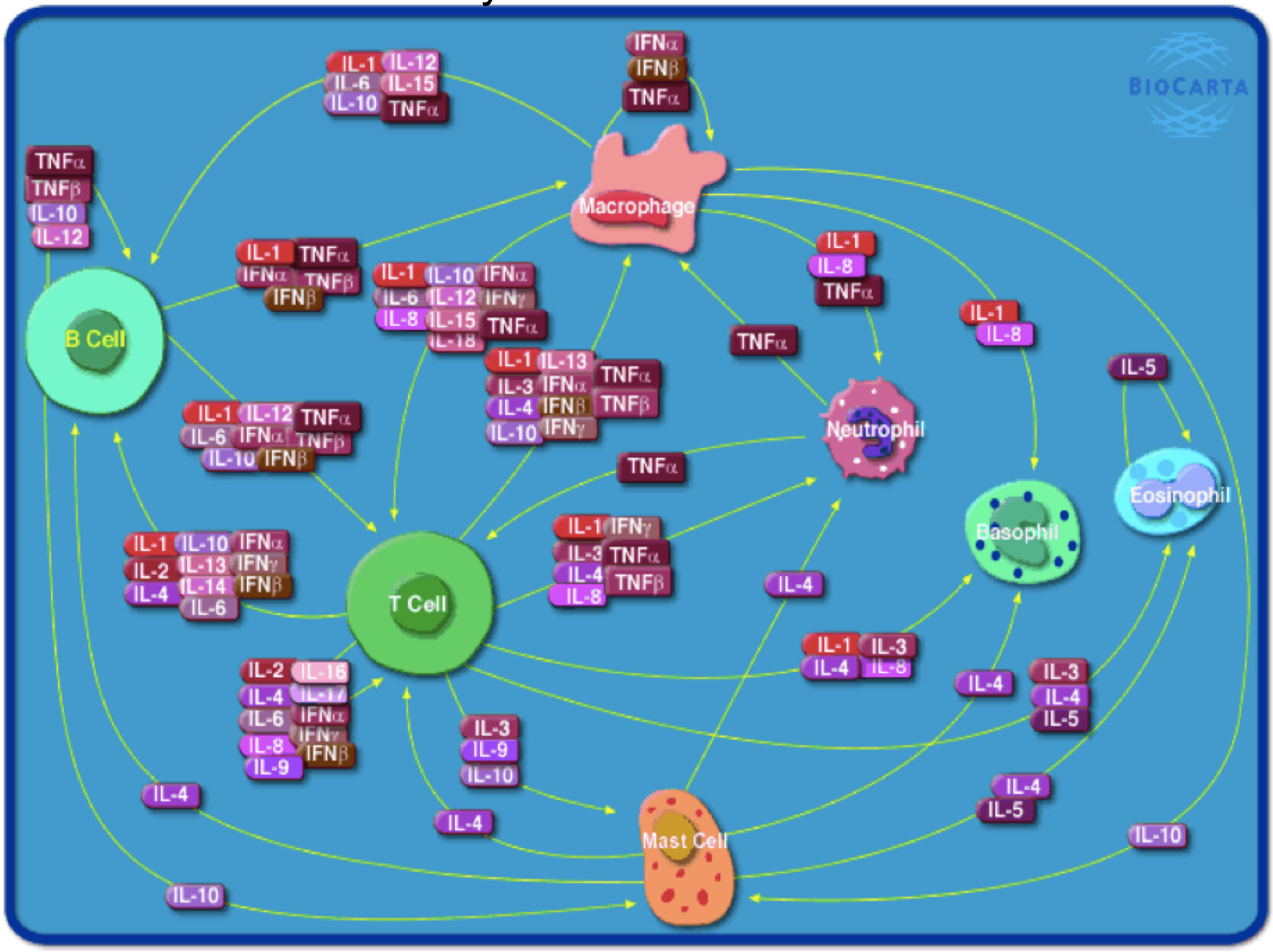


Le citochine

Le citochine sono polipeptidi prodotti in risposta a microbi e antigeni e hanno il ruolo di mediare e regolare le risposte immuni e infiammatorie.



The cytokine network



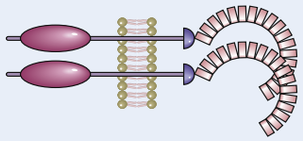
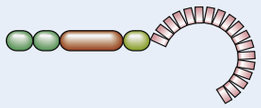
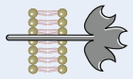
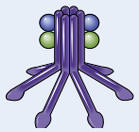
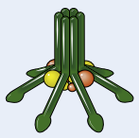
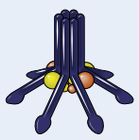
V. Cytokines

Cytokine	Size	Principal Cell Source	Principal Cellular Targets and Biologic Effects
Tumor necrosis factor (TNF)	17 kD; 51-kD homotrimer	Macrophages, T cells	Endothelial cells: activation (inflammation, coagulation) Neutrophils: activation Hypothalamus: fever Muscle, fat: catabolism (cachexia) Many cell types: apoptosis
Interleukin-1 (IL-1)	17-kD mature form; 33-kD precursors	Macrophages, endothelial cells, some epithelial cells	Endothelial cells: activation (inflammation, coagulation) Hypothalamus: fever Liver: synthesis of acute-phase proteins T cells: T_H17 differentiation
Chemokines (see Table 3-2)	8-12 kD	Macrophages, endothelial cells, T cells, fibroblasts, platelets	Leukocytes: chemotaxis, activation; migration into tissues
Interleukin-12 (IL-12)	Heterodimer of 35-kD and 40-kD subunits	Macrophages, dendritic cells	T cells: T_H1 differentiation NK cells and T cells: IFN-γ synthesis, increased cytotoxic activity
Type I interferons (IFN-α, IFN-β)	IFN-α: 15-21 kD IFN-β: 20-25 kD	IFN-α: macrophages, plasmacytoid dendritic cells IFN-β: fibroblasts	All cells: antiviral state, increased class I MHC expression NK cells: activation
Interleukin-10 (IL-10)	Homodimer of 34-40-kD and 18-kD subunits	Macrophages, T cells (mainly regulatory T cells)	Macrophages, dendritic cells: inhibition of IL-12 production and expression of costimulators and class II MHC molecules
Interleukin-6 (IL-6)	19-26 kD	Macrophages, endothelial cells, T cells	Liver: synthesis of acute-phase proteins B cells: proliferation of antibody-producing cells T cells: T_H17 differentiation
Interleukin-15 (IL-15)	13 kD	Macrophages, others	NK cells: proliferation T cells: proliferation (memory $CD8^+$ cells)
Interleukin-18 (IL-18)	17 kD	Macrophages	NK cells and T cells: IFN-γ synthesis
Interleukin-23 (IL-23)	Heterodimer of unique 19-kD subunit and 40-kD subunit of IL-12	Macrophages and dendritic cells	T cells: maintenance of IL-17–producing T cells
Interleukin-27 (IL-27)	Heterodimer of 28-kD and 13-kD subunits	Macrophages and dendritic cells	T cells: T_H1 differentiation; inhibition of T_H17 cells NK cells: IFN-γ synthesis

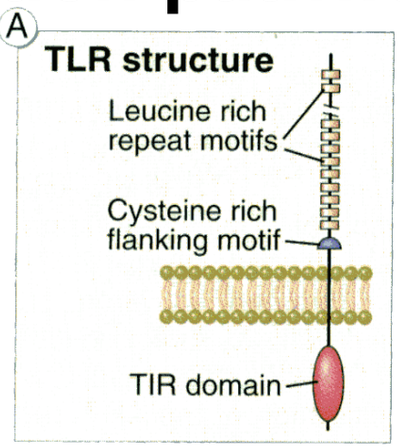
Pattern recognition molecules of the innate immune system

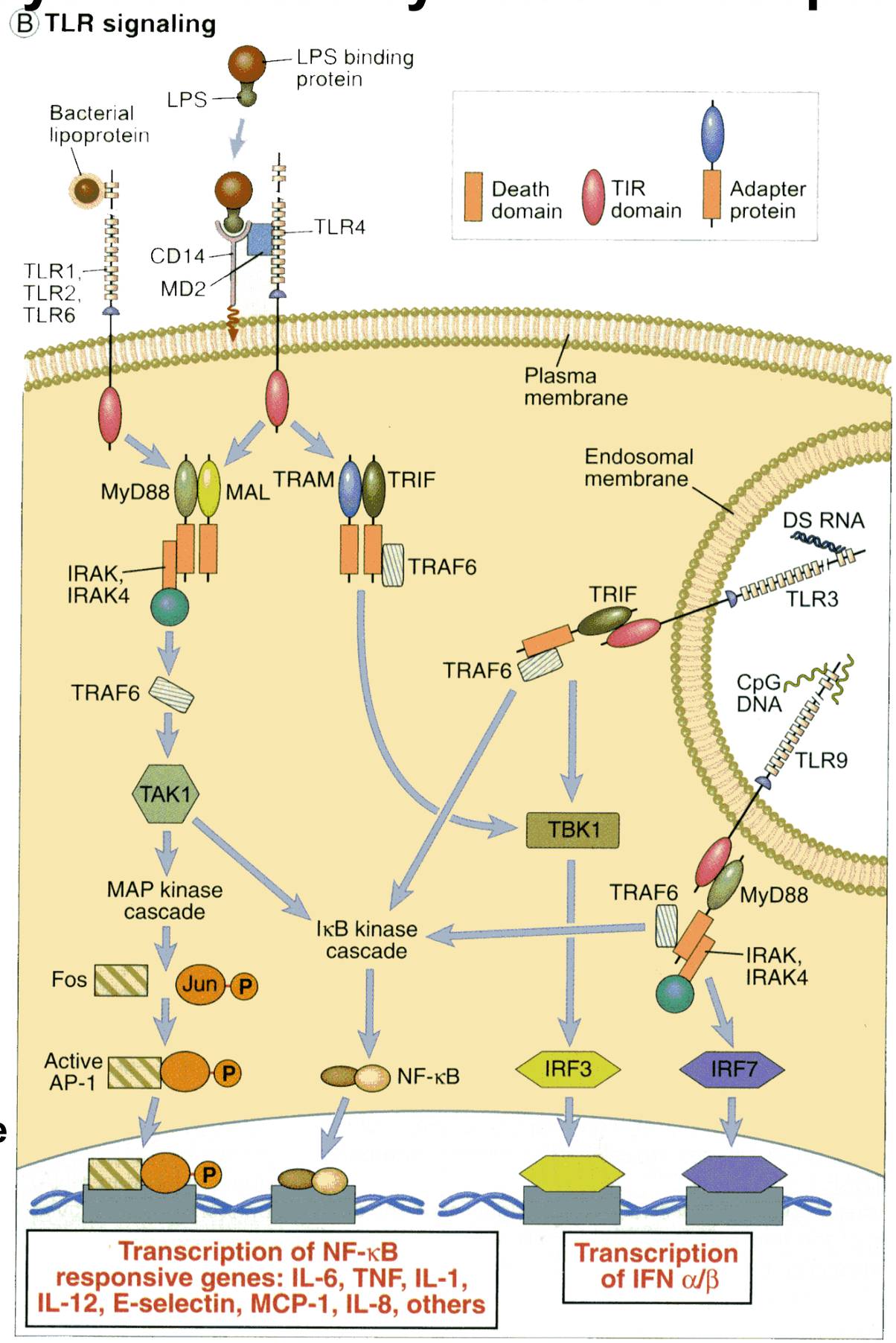
NOD-like receptors (NLRs): nucleotide-binding oligomerization domain-like receptors

RIG-I-like receptors: retinoic acid-inducible gene-I-like receptors

Pattern Recognition Receptors	Location	Specific Examples	PAMP/DAMP Ligands
Cell-Associated			
Toll-like receptors (TLRs) 	Plasma membrane and endosomal membranes of dendritic cells, phagocytes, B cells, endothelial cells, and many other cell types	TLRs 1-9	Various microbial molecules including bacterial LPS and peptidoglycans, viral nucleic acids
NOD-like receptors (NLRs) 	Cytosol of phagocytes, epithelial cells, and other cells	NOD1/2 NLRP family (inflammasomes)	Bacterial cell wall peptidoglycans Intracellular crystals (urate, silica); changes in cytosolic ATP and ion concentrations; lysosomal damage
RIG-like receptors (RLRs) 	Cytosol of phagocytes and other cells	RIG-1, MDA-5	Viral RNA
Cytosolic DNA sensors (CDSs) 	Cytosol of many cell types	AIM2; STING-associated CDSs	Bacterial and viral DNA
C-type lectin–like receptors (CLRs) 	Plasma membranes of phagocytes	Mannose receptor Dectin	Microbial surface carbohydrates with terminal mannose and fructose Glucans present in fungal cell walls
Scavenger receptors 	Plasma membranes of phagocytes	CD36	Microbial diacylglycerides
N-Formyl met-leu-phe receptors 	Plasma membranes of phagocytes	FPR and FPRL1	Peptides containing *N*-formylmethionyl residues
Soluble			
Pentraxins 	Plasma	C-reactive protein	Microbial phosphorylcholine and phosphatidylethanolamine
Collectins 	Plasma	Mannose-binding lectin	Carbohydrates with terminal mannose and fructose
	Alveoli	Surfactant proteins SP-A and SP-D	Various microbial structures
Ficolins 	Plasma	Ficolin	*N*-Acetylglucosamine and lipoteichoic acid components of the cell walls of gram-positive bacteria
Complement 	Plasma	Various complement proteins	Microbial surfaces

Signal transduction pathways activated by Toll-like receptors





MD2 = proteina accessoria
TIR = Toll-interleukin-1 receptor
TRIF = TIR domain-containing adapter inducing interferon beta
TRAM = TRIF-related adapter molecule
MAL = MyD88 adapter-like
IRAK = IL-1 receptor-associated kinase
TRAF = TNF receptor-associated factor
TAK = TGFbeta-activated kinase
IkB = inhibitory protein of NF-kB
IKK = IkB kinasi
NF-kB = nuclear factor of kappa light chain gene enhancer in B-cells
TBK = TRAF family member associated NF-kB activator binding kinase
IRF = interferon response factor
AP = Activator protein (formato dalle proteine jun e fos)
MAP-mitogen associated protein

nature Vol 437|13 October 2005|doi:10.1038/nature03985

LETTERS

A network-based analysis of systemic inflammation in humans

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Inflammation and Host Response to Injury Large Scale Collaborative Research Program Paul E. Bankey[1], Timothy R. Billiar[2], David G. Camp[3], George Casella[4], Irshad H. Chaudry[5], Mashkoor A. Choudhry[5], Charles Cooper[26], Asit De[1], Constance Elson[6], Bradley Freeman[7], Richard L. Gamelli[8], Celeste Campbell-Finnerty[9], Nicole S. Gibran[10], Douglas L. Hayden[6], Brian G. Harbrecht[2], David N. Herndon[9], Jureta W. Horton[11], William J. Hubbard[5], John L. Hunt[12], Jeffrey Johnson[13], Matthew B. Klein[14], James A. Lederer[15], Tanya Logvinenko[6], Ronald V. Maier[10], John A. Mannick[15], Philip H. Mason[26], Bruce A. McKinley[16], Joseph P. Minei[11], Ernest E. Moore[13], Frederick A. Moore[16], Avery B. Nathens[10], Grant E. O'Keefe[10], Laurence G. Rahme[17], Daniel G. Remick[18], David A. Schoenfeld[6], Martin Schwacha[5], Michael B. Shapiro[19], Geoffrey M. Silver[8], Richard D. Smith[3], John D. Storey[20], Mehmet Toner[21], H. Shaw Warren[22], Michael A. West[19]

Aim: identify the mechanisms responsible for the systemic inflammatory response to LPS in the context of complete recovery

Questo studio NON può essere eseguito su cellule

Questo studio NON può essere eseguito su pazienti “veri” in quanto i pazienti con endotossiemia hanno spesso patologie pregresse oppure vanno incontro a trattamenti che alterano la risposta infiammatoria

APPLICATION PHASES:

1. Human subjects and induction of endotoxemia

2. The dynamics of the genomic inflammatory response

3. Interactome building

4. The systemic inflammatory network

5. Analysis of the dynamics of inflammation pathways

6. Conclusions

1. Human subjects and induction of endotoxemia

a. The model of human endotoxemia:

8 soggetti sani tra 18-40 anni sono stati divisi in 2 gruppi: controllo e trattati con LPS 2ng/kg

b. Blood sampling:

I campioni di sangue sono stati ottenuti da ogni paziente a tempo 0, e a 2h, 4h, 6h, 9h e 24h dopo l'infusione di LPS (dynamic analysis)

c. Obtainment of total blood leukocytes and extraction of RNA

- Isolamento dei leucociti dopo la lisi dei globuli rossi
- Isolamento del RNA totale mediante kit Qigen

2. The dynamics of the genomic inflammatory response

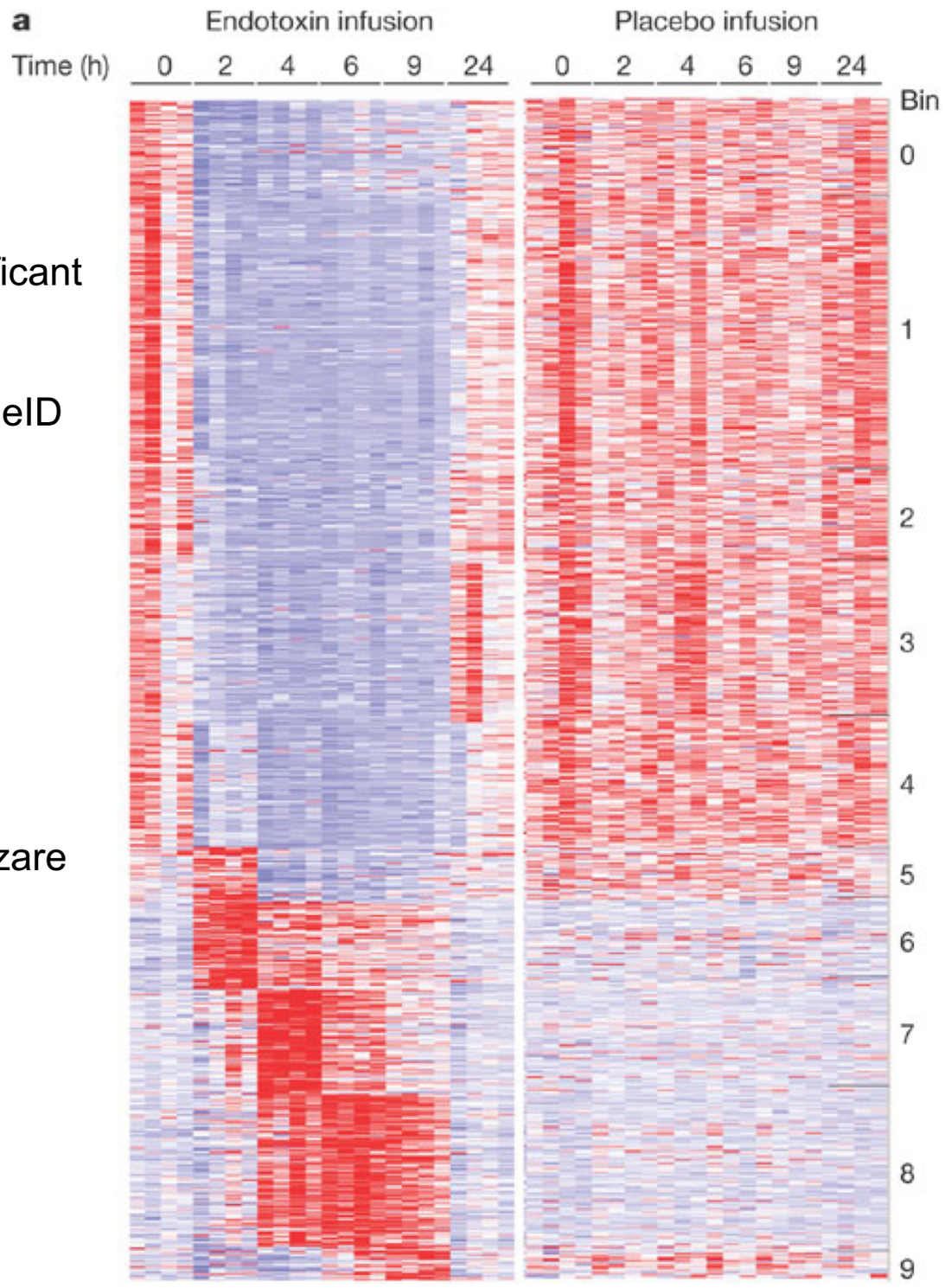
Profili di espressione genica nei leucociti circolanti in risposta all'endotossina

Results form micorarrays:

- 5.093 probe sets vary in a significant manner LPS

- identified**3.714 geni** EntrezGeneID (http://www.ncbi.nih.gov/Entrez/)

The clustering of probe sets in 10 bins was made with K-means analysis using Cluster and TreeView (che rappresentano due programmi integrati per analizzare e visualizzare risultati di esperimenti complessi di microarrays).



Ogni bin rappresenta un pattern temporale distinto

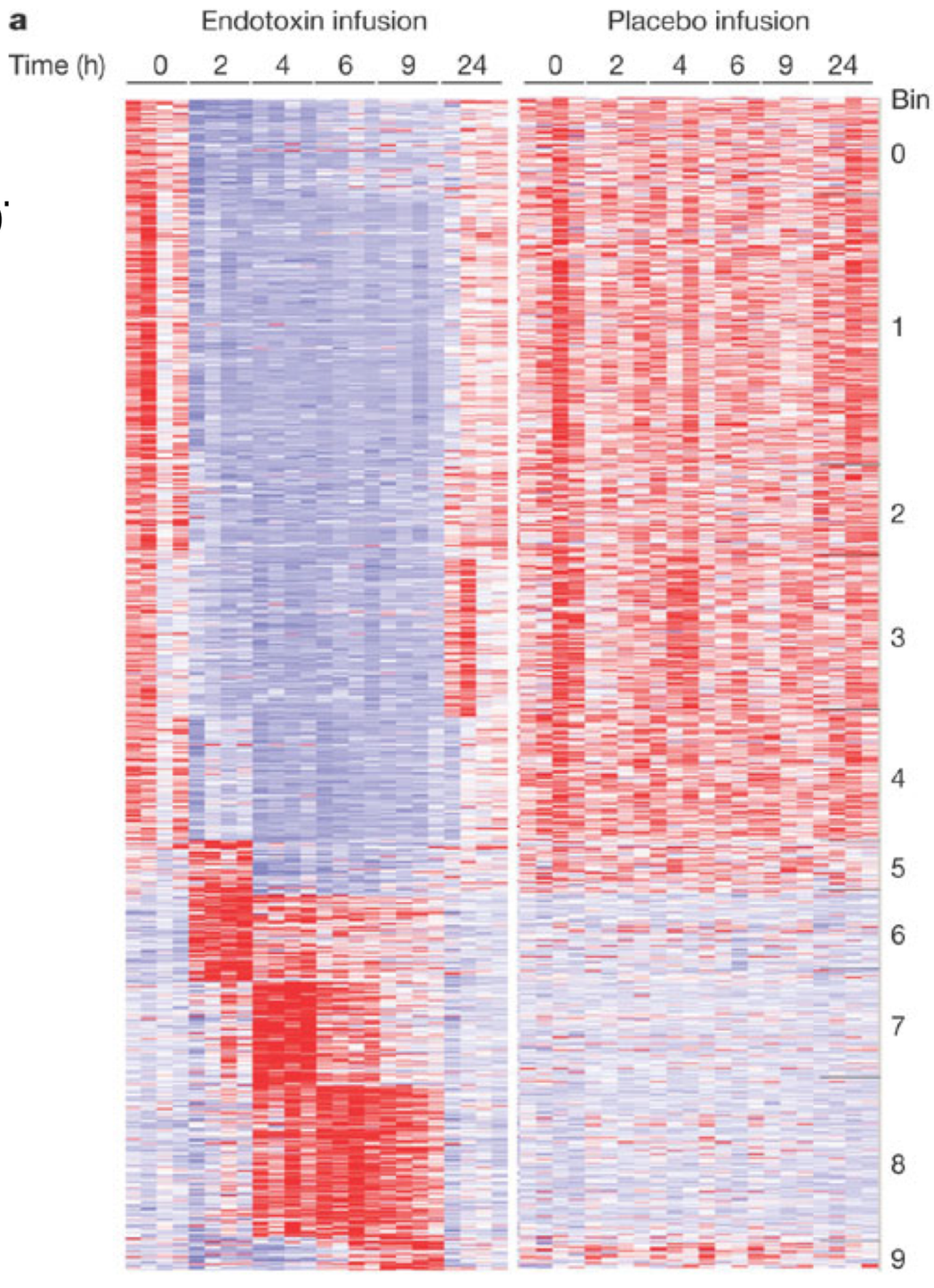
2. The dynamics of the genomic inflammatory response

Results:

More than half of genes show reduction o
expression (bins 0-4)

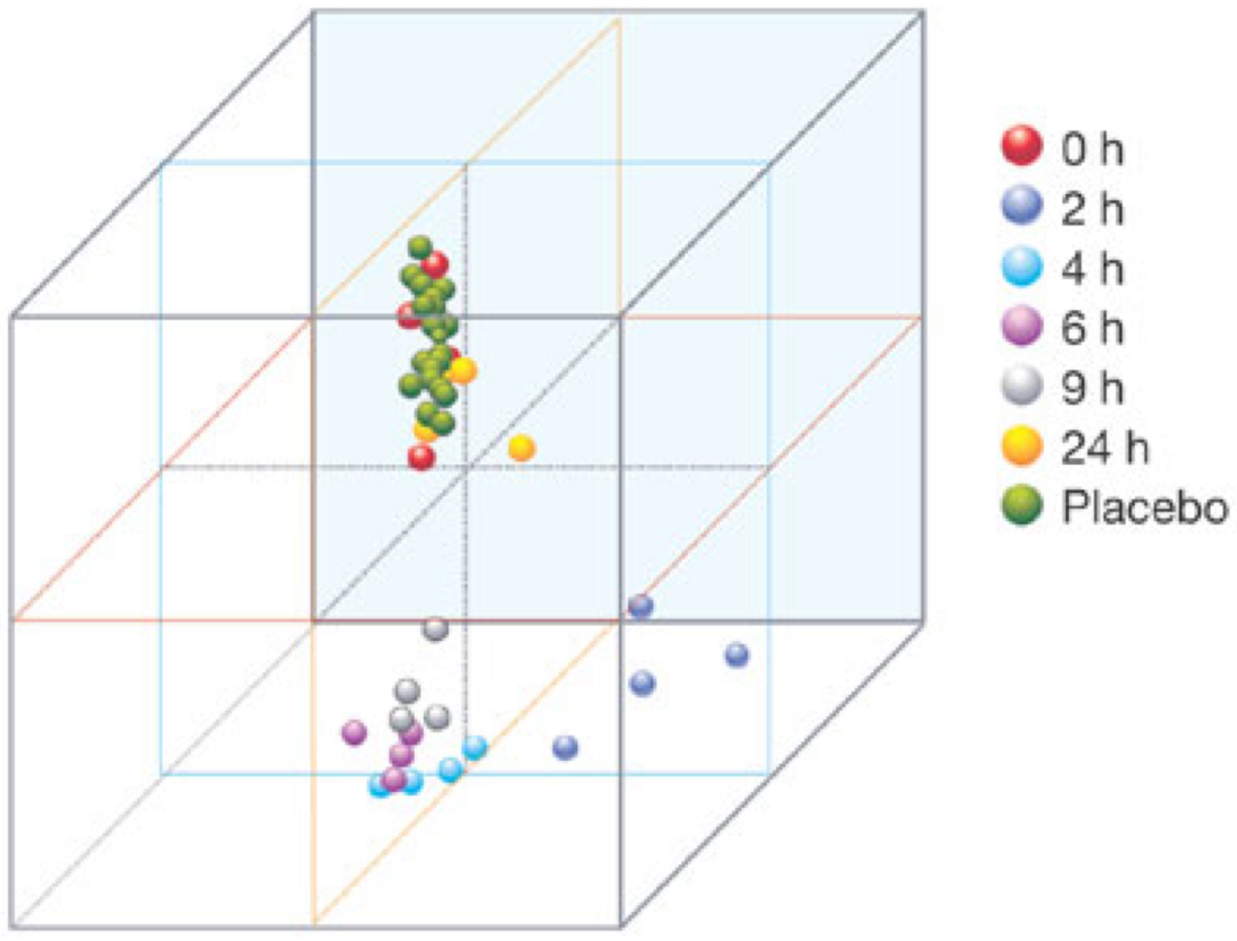
One small group shows an increase of
expression at 2h (bins 5, 6)

The expression of other genes increases
at later time points (bins 7-9)



2. The dynamics of the genomic inflammatory response

3D plot del principal component dei probe sets significativi a vari time points dopo la somministrazione di LPS



PRINCIPAL COMPONENT ANALYSIS per dati di microarays

Principal components analysis (PCA) **is a statistical technique for determining the key variables in a multidimensional data set that explain the differences in the observations,** and can be **used to simplify the analysis and visualization of multidimensional data sets.** PCA allows us to **summarize the ways in which gene responses vary under different conditions.**

PCA **is a method that reduces data dimensionality** by performing a covariance analysis between factors. As such, **it is suitable for data sets in multiple dimensions, such as a large experiment in gene expression**.

3. Interactome building

The DATABASE

http://www.ingenuity.com/

Sono state utilizzate le informazioni fornite dal **database di Ingenuity Systems Inc.** (a pagamento!)

2005: "**The Ingenuity Pathways Knowledge Base** (KB) is the largest curated database of previously published findings on mammalian biology from the public literature.
The KB is constructed through the efforts of Ph.D.-level scientists who have read the abstracts of every paper in the Ingenuity KB. These scientists manually extracted the findings in the KB from the full text of >200,000 articles, including the abstract, text, tables, and figures.

As of January 2005, the KB includes information of more than 9,800 human (including the ~9,500 Reviewed and Validated Human RefSeqs, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?CMD=search&DB=gene), 7,900 mouse, and 5,000 rat genes."

3. Interactome building

The DATABASE

http://www.ingenuity.com/

2011: The Ingenuity Pathways Analysis (IPA) program is a software that helps researchers model, analyze, and understand data derived from gene expression, microRNA, and SNP microarrays; metabolomics, proteomics, and RNA-Seq experiments; and small-scale experiments that generate gene and chemical lists**.**

Network analysis was performed on molecular relationships involving 8,000 human orthologs (between human, mouse and rat, as defined by **Homologene**, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=homologene).

IPA It's just good science.

INGENUITY® SYSTEMS

Applications

- Target Identification and Validation
- Biomarker Discovery
- Drug Mechanism of Action
- Drug Mechanism of Toxicity
- Disease Mechanisms

Experimental approaches supported

- RNA-Seq
- microarray
- microRNA
- mRNA
- qPCR
- proteomics
- genotyping

Identifiers supported in IPA

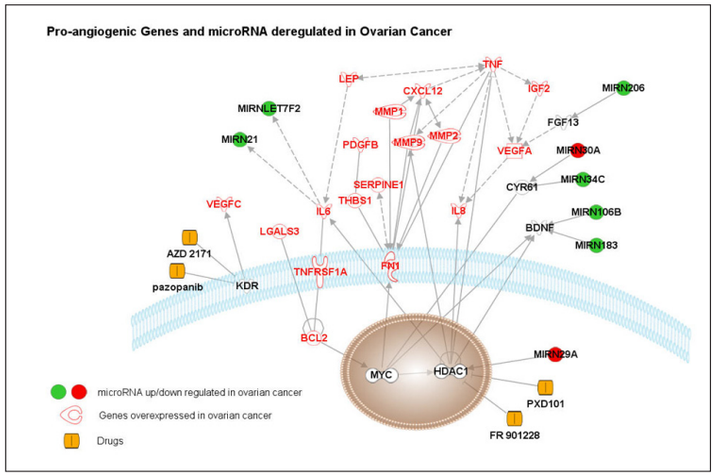
- Affymetrix (Exon/Gene Expression, 3' IVT Expression)
- Affymetrix SNP ID (Genotyping)
- Agilent (Gene Expression, microRNA)
- Applied Biosystems (Gene Expression, microRNA)
- CAS Registry
- CodeLink
- dbSNP IDs (including Illumina genotyping arrays with dbSNP ids)
- Entrez Gene
- Ensembl *new*
- GenBank
- GenPept
- GI Number
- HUGO Gene Symbol
- Human Metabolome Database (HMDB)
- Illumina (whole-genome & microRNA arrays)
- International Protein Index
- KEGG ID
- miRBase (mature)
- PubChem CID
- RefSeq *new*
- UCSC Human Isoform IDs (hg 18 & hg 19)
- UniGene
- UniProt/SwissProt Accession

Species-specific identifiers supported in IPA

- Human
- Mouse
- Rat
- Additional species supported

IPA® 9.0

IPA® is an all-in-one, web-based software application that enables you to analyze, integrate, and understand data derived from gene expression, microRNA, and SNP microarrays; metabolomics, proteomics, and RNA-Seq experiments; and small-scale experiments that generate gene and chemical lists. With IPA you can search for targeted information on genes, proteins, chemicals, and drugs, and build interactive models of your experimental systems. IPA's data analysis and search capabilities help you understand the significance of your data, specific target, or candidate biomarker in the context of larger biological or chemical systems, backed by the Ingenuity® Knowledge Base of highly structured, detail-rich biological and chemical Findings.



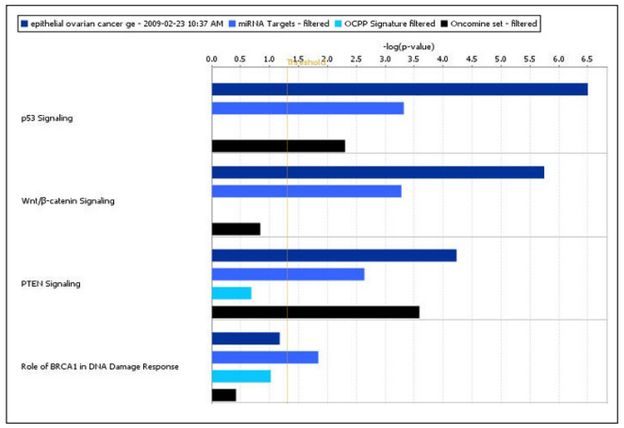
Path Designer transforms networks and pathways into publication quality representations of biological systems.

Data Analysis & Interpretation

IPA's Data Analysis and Interpretation unlocks the insights buried in experimental data by quickly identifying relationships, mechanisms, functions, and pathways of relevance, allowing you to move beyond statistical analysis to novel biological insights, testable hypotheses, and validation experiments.

IPA Core Analysis delivers a rapid assessment of the signaling and metabolic pathways, molecular networks, and biological processes that are most significantly perturbed in a dataset of interest.

- Understand the relative impact of changes in mRNA, microRNA, protein or metabolite levels in the context of well-characterized pathways.
- Identify the cellular and disease phenotypes most significant to a set of genes, and understand how those genes impact that phenotype, i.e. whether they increase or decrease a biological process.



Identify pathways implicated by multiple experimental platforms.

- Optimize visualization and biological context of analyses with Context and Network Size parameters.

HomoloGene
Homepage
Query Tips
Build Procedure
FTP site

Genome Resources
Homo sapiens
Mus musculus
Rattus norvegicus
Danio rerio

HomoloGene is a system for automated detection of homologs among the annotated genes of several completely sequenced eukaryotic genomes.

HomoloGene Release 65 Statistics

Initial numbers of genes from complete genomes, numbers of genes placed in a homology group, and the numbers of groups for each species.

Species	Number of Genes		HomoloGene groups
	Input	Grouped	
Homo sapiens	19,943*	18,981	18,431
Pan troglodytes	25,096	16,850	15,980
Canis familiaris	19,766	16,708	15,951
Bos taurus	22,049	18,180	16,224
Mus musculus	25,388	21,766	19,005
Rattus norvegicus	21,991	19,229	17,473
Gallus gallus	17,959	13,142	11,905
Danio rerio	26,690*	21,084	14,067
Drosophila melanogaster	13,827*	9,282	7,749
Anopheles gambiae	12,460	8,867	7,541
Caenorhabditis elegans	20,132*	8,678	4,810
Schizosaccharomyces pombe	5,043	3,225	2,935
Saccharomyces cerevisiae	5,880	4,851	4,370
Kluyveromyces lactis	5,335	4,459	4,382
Eremothecium gossypii	4,722	3,928	3,884
Magnaporthe grisea	12,832	7,330	6,399
Neurospora crassa	9,821*	6,287	6,144
Arabidopsis thaliana	27,309*	19,961	11,243
Oryza sativa	26,887	17,276	10,627
Plasmodium falciparum	5,266	1,862	799

'*' indicates organisms where new genome annotation data is used in this build.
Last updated on: Mon Feb 14 2011

We have recently adopted a new build procedure that makes use of amino acid sequence searching (blastp) to find more distant relationships, but the procedure still refers to the DNA sequence for computation of some of the statistics. The matching strategy is guided by the taxonomic tree such that more closely related organisms are compared first. Moreover, HomoloGene entries now include paralogs in addition to orthologs.

What's New

HomoloGene release 65 includes updated annotations for the following species: Homo sapiens (NCBI release 37.2), Danio rerio (NCBI release 4.1), Drosophila melanogaster (NCBI release 9.3) Caenorhabditis elegans (NCBI release 9.1), Arabidopsis thaliana (NCBI release 9.1).

Tip of The Day

Use [unigene id] in your search query to restrict search results to that particular unigene cluster. e.g. Hs.15484[unigene id].
[More Tips]

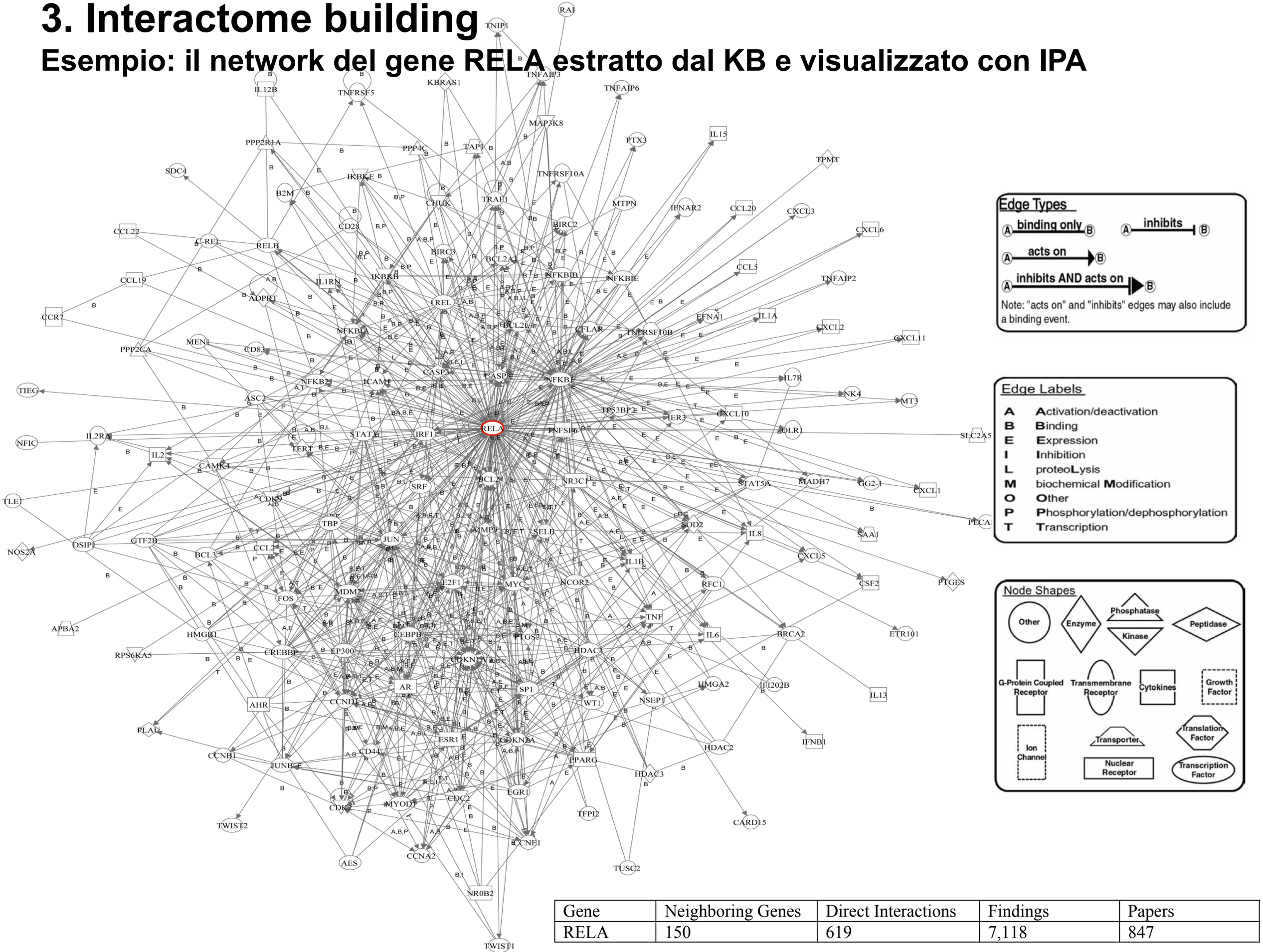
Related Resources

Entrez Genomes

A collection of complete genome sequences that includes more than 1000 viruses and over hundred microbes
- Archaea
- Bacteria
- Eukaryota
- Viruses

3. Interactome building

Esempio: il network del gene RELA estratto dal KB e visualizzato con IPA



Edge Types

- A — binding only — B
- A — inhibits — B
- A — acts on → B
- A — inhibits AND acts on → B

Note: "acts on" and "inhibits" edges may also include a binding event.

Edge Labels

A	**A**ctivation/deactivation
B	**B**inding
E	**E**xpression
I	**I**nhibition
L	proteo**L**ysis
M	biochemical **M**odification
O	**O**ther
P	**P**hosphorylation/dephosphorylation
T	**T**ranscription

Node Shapes

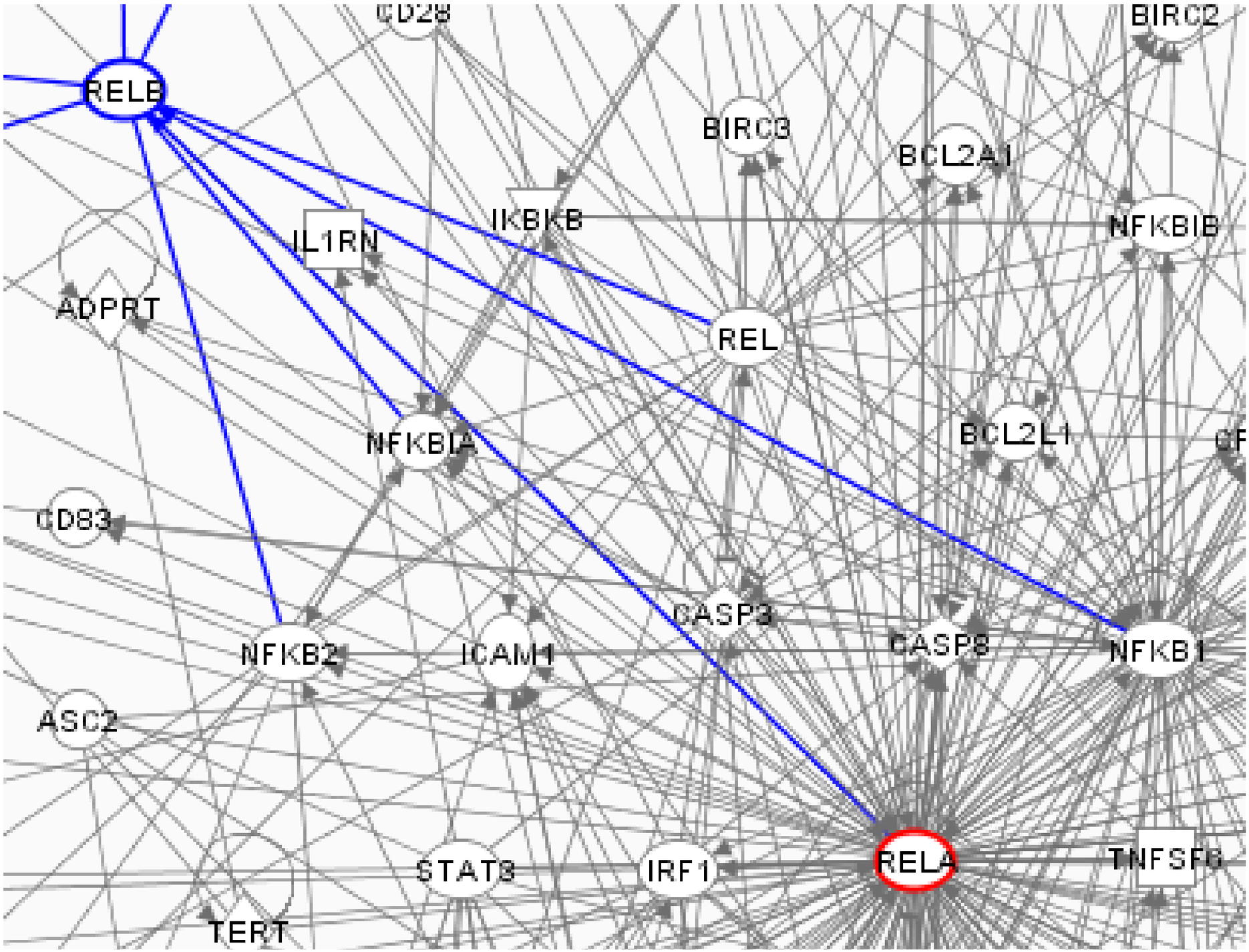
Other · Enzyme · Phosphatase · Kinase · Peptidase · G-Protein Coupled Receptor · Transmembrane Receptor · Cytokines · Growth Factor · Ion Channel · Transporter · Translation Factor · Nuclear Receptor · Transcription Factor

Gene	Neighboring Genes	Direct Interactions	Findings	Papers
RELA	150	619	7,118	847

NF-kB = nuclear factor of kappa light chain gene enhancer in B-cells

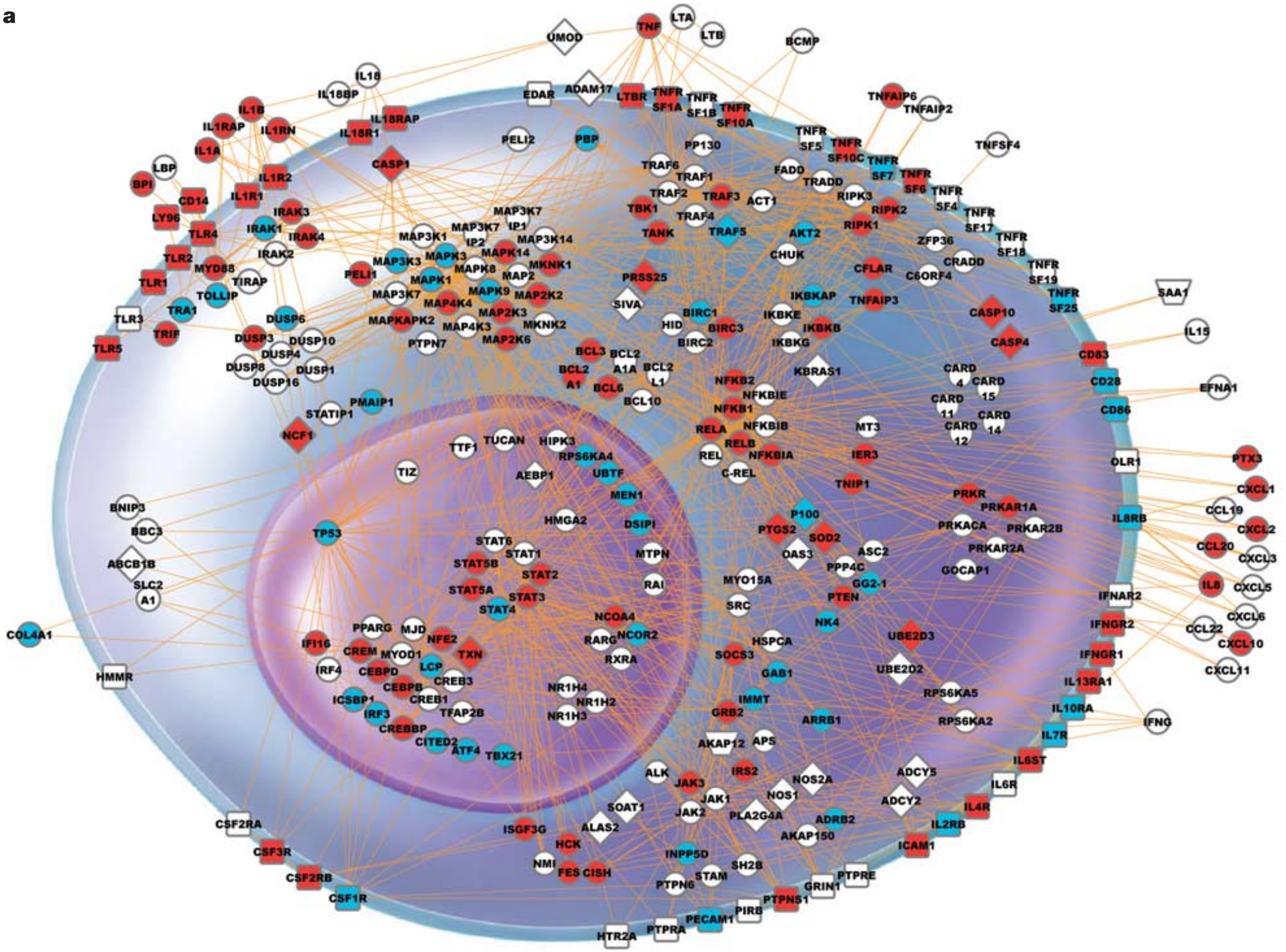
Rel/NFKB family includes REL (c-Rel) (MIM164910), RELA (RelA/p65) (MIM 164014), RELB (RelB) (604758), NFKB1 (P105/p50) (MIM 164011), and NFKB2 (p100/p52) (MIM 164012).

NFKB is activated by a wide variety of stimuli such as cytokines, oxidant-free radicals, inhaled particles, ultraviolet irradiation, and bacterial or viral products. Inappropriate activation of NF-kappa-B has been linked to inflammatory events associated with autoimmune arthritis, asthma, septic shock, lung fibrosis, glomerulonephritis, atherosclerosis, and AIDS.



4. The systemic inflammatory network

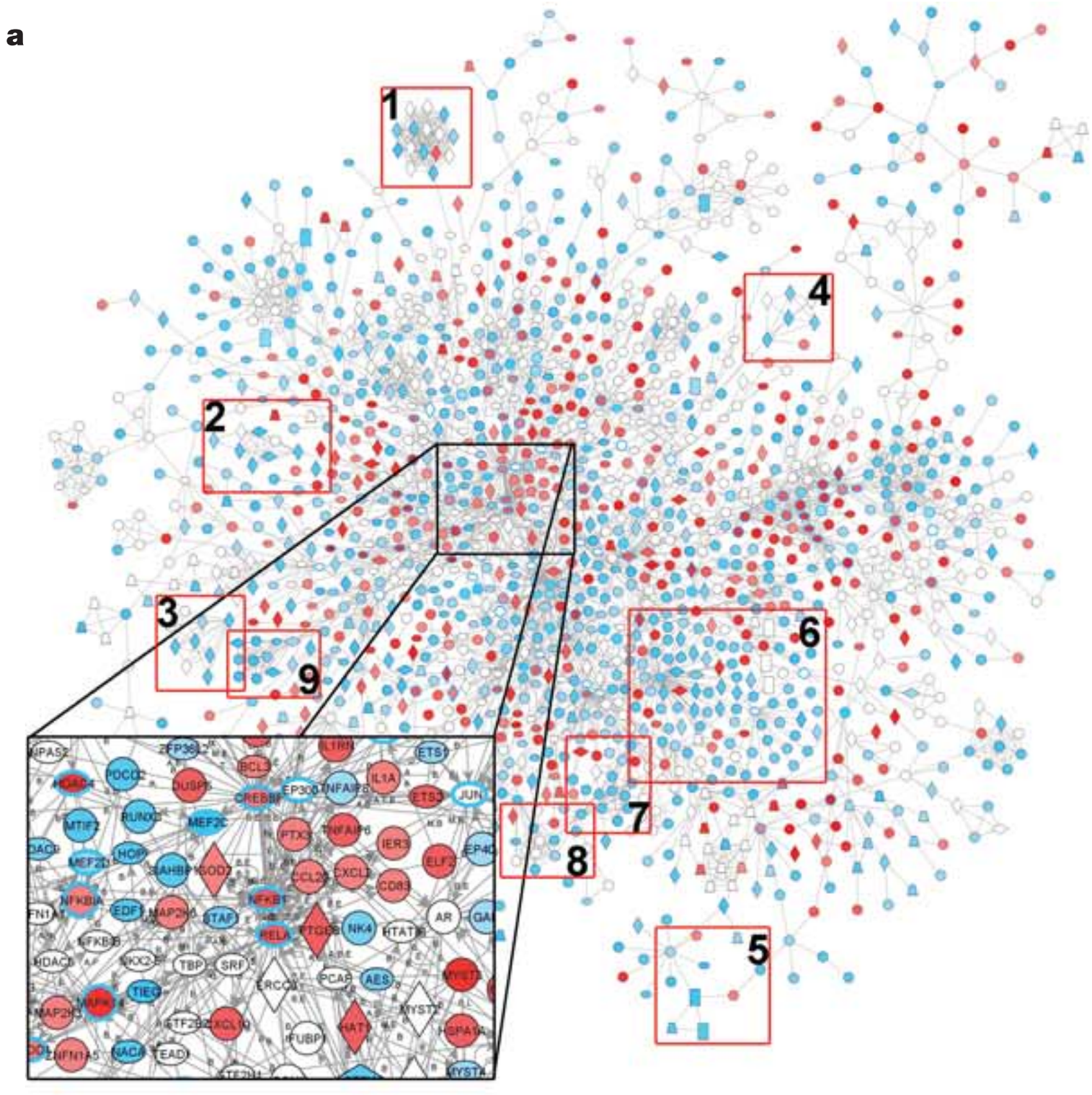
A. THE VIRTUAL INFLAMMATORY CELL: the specific response of the innate immunity cell



292 representative genes involved in inflammation and innate immunity. Genes for which the expression statistically increased from baseline are coloured red, those for which expression decreased are shown in blue

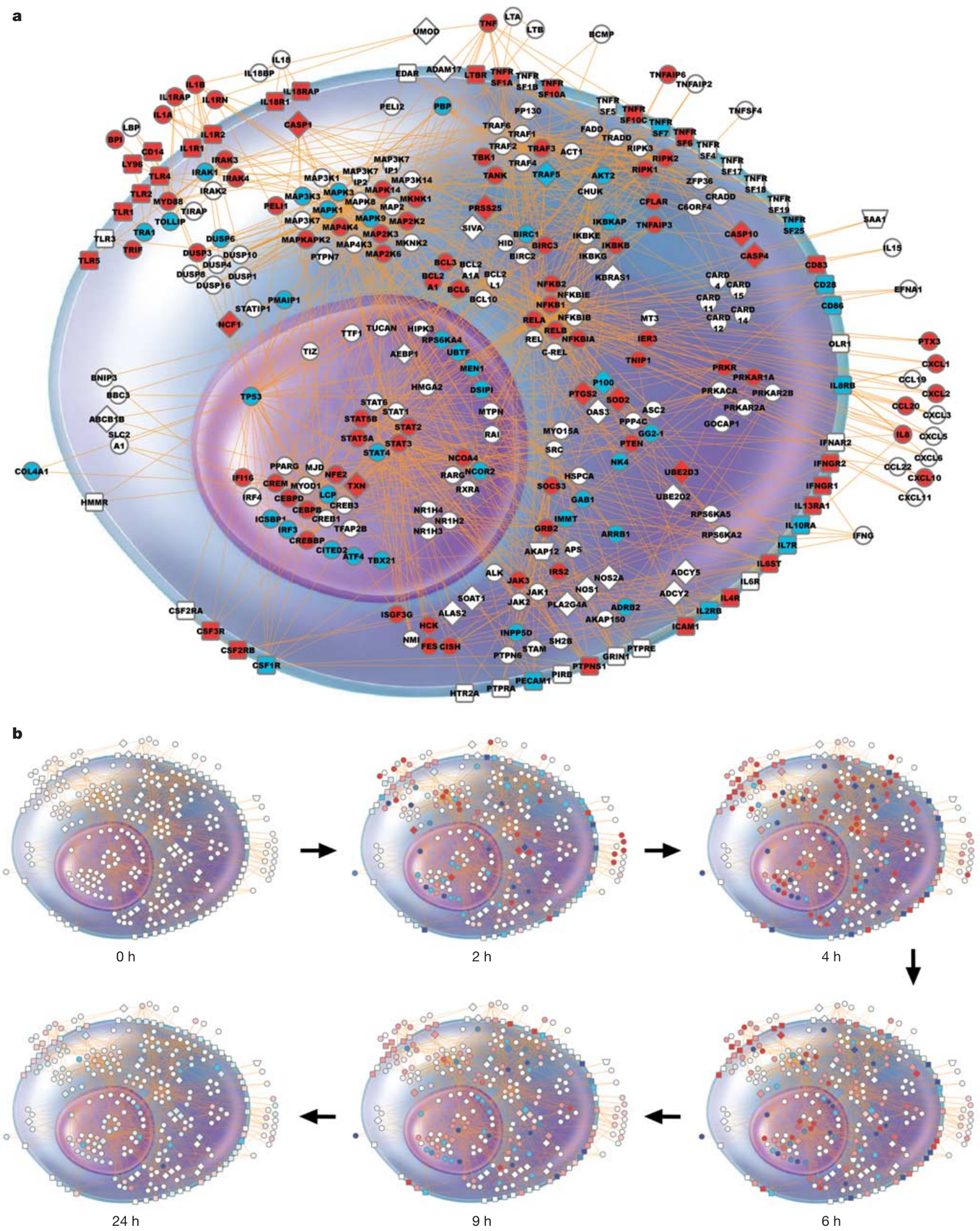
4. The systemic inflammatory network

B. The intracellular network of the inflammatory response
(formed by 1.556 genes)



5. Analysis of the dynamics of inflammation pathways

Analysis of pathways of representative genes of the innate immunity pathways in the virtual cell



5. Analysis of the dynamics of inflammation pathways

The virtual cell: Results

2-4h

- Espressione massima di citochine e chemochine proinfiammatorie: TNFSF2 (TNFa), IL1alpha, IL1beta, CXCL1 (GROalpha), CXCL2 (GRO-beta), CXCL8 (IL-8) and CXCL10
- Espressione di molecole pro-infiammatorie come PTGS2 (sintesi di prostaglandine),
- Espressione di SOD2, formazione di ROS (reactive oxygen species) come H2O2
- Espressione di TLRs
- Espressione di fattori di trascrizione pro-infiammatori a 2-4h: membri della famiglia di nuclear factor kappa/RelA (NFKB1, NFKB2, RELA and RELB) e STAT
- Espressione di geni per fattori di trascrizione che limitano la risposta innata come per esempio **s**uppressor **o**f **c**ytokine **s**ignalling 3 (SOCS3).

TNSF2 = Tumor necrosis factor ligand superfamily member 2 = TNFalpha
PTGS2 = Prostaglandin G/H synthase 2 and Cyclooxygenase-2
SOD2 = **Superoxide dismutase [Mn], mitochondrial**
STAT = Signal Transducer and Activator of Transcription

5. Analysis of the dynamics of inflammation pathways

The virtual cell: Results

6h

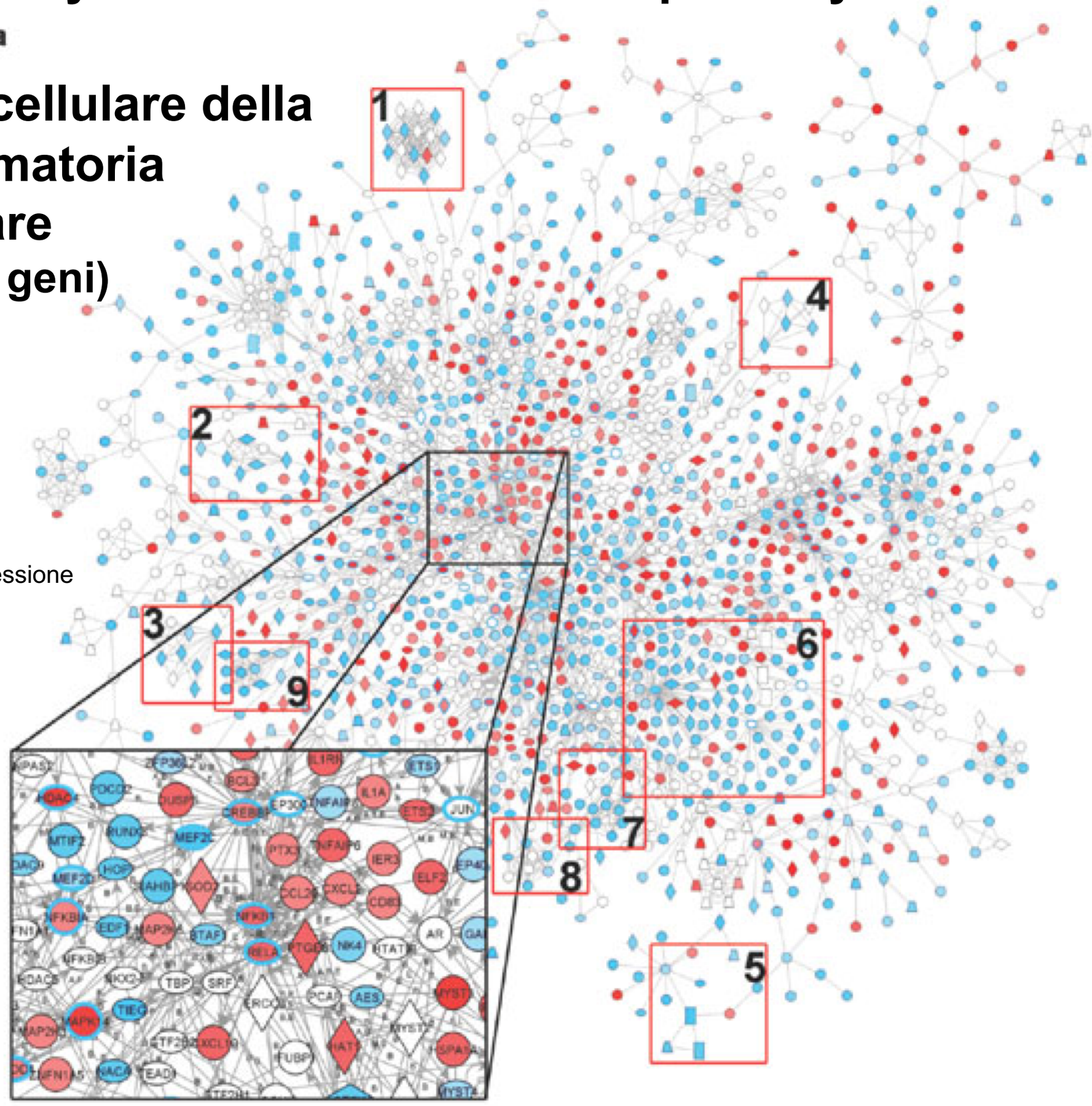
- Espressione di geni per STAT (signal transductor and activator of transcription) e cAMP-response element-binding protein (CREB) genes.
- Espressione di geni per fattori di trascrizione che limitano la risposta innata come per esempio **s**uppressor **o**f **c**ytokine **s**ignalling 3 (SOCS3).
- Espressione per TLRs
- Riduzione dell'espressioni di geni pro-infiammatori upregolati a 4h

9h – Riduzione dei geni pro-infiammatori

24h – Ritorno ad uno stato simile alla fase iniziale (tempo 0)

5. Analysis of the dynamics of inflammation pathways

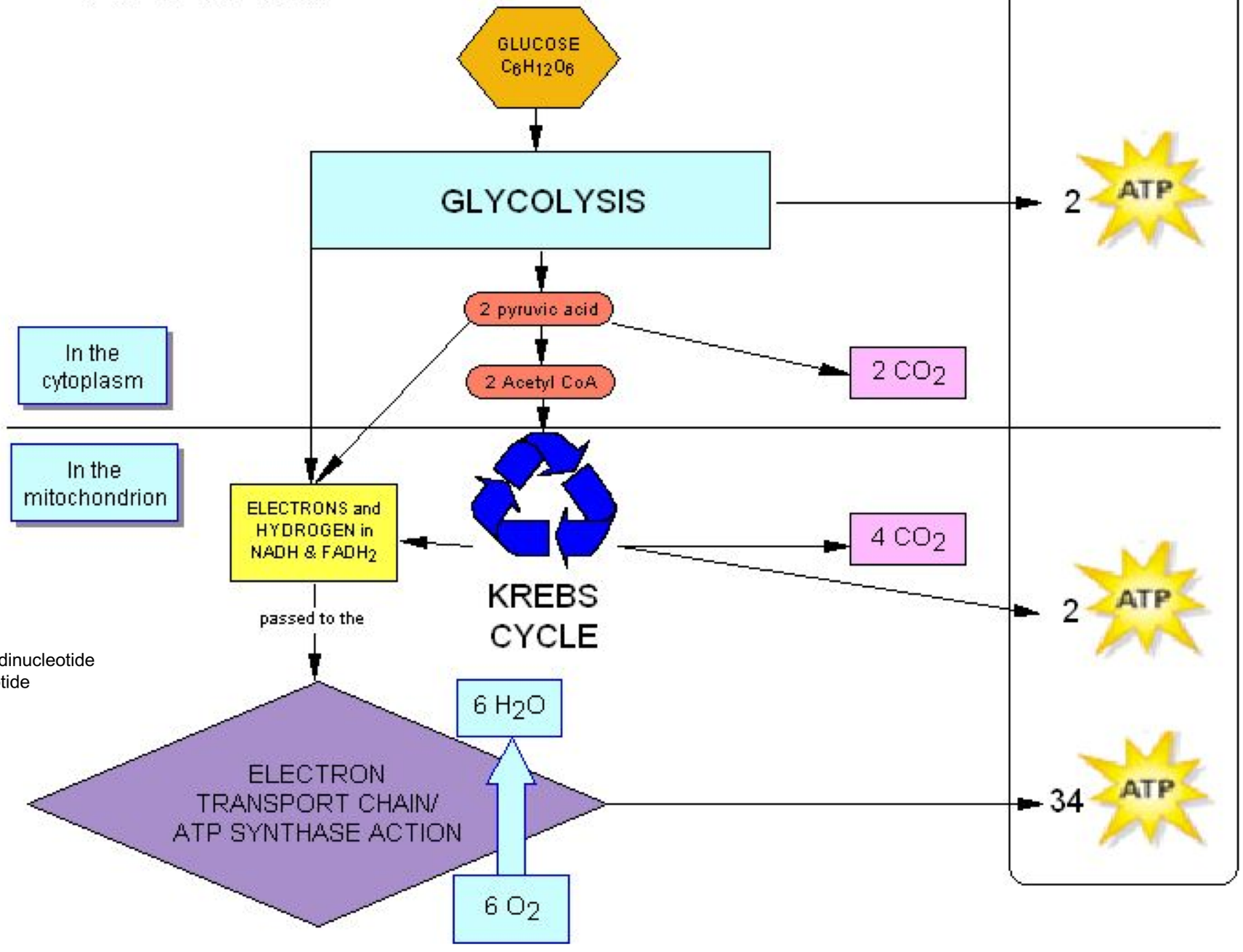
Il network intracellulare della risposta infiammatoria generale cellulare (formato da 1.556 geni)



Blu = geni con ridotta espressione
Rosso = geni con aumentata espressione

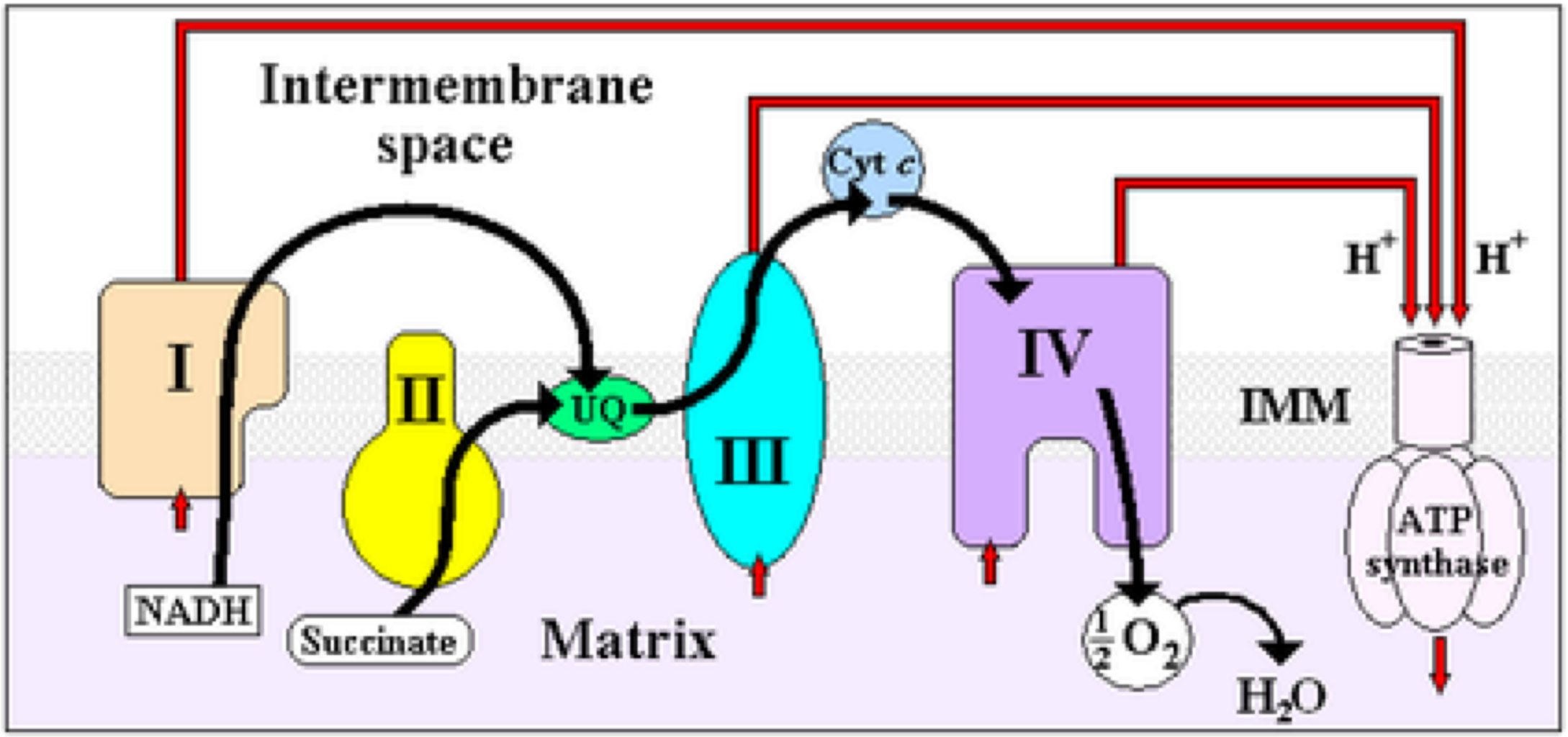
Cellular Respiration: An Overview

$C_6H_{12}O_6 + 6O_2 \Rightarrow\Rightarrow 6CO_2 + 6\,H_2O +$ about 38 ATP



NAD = Nicotinamide adenine dinucleotide
FAD = flavin adenine dinucleotide

The electron transport chain (ETC) in mitochondria



NAD = Nicotinamide adenine dinucleotide
UQ = ubiquinone
FAD = flavin adenine dinucleotide

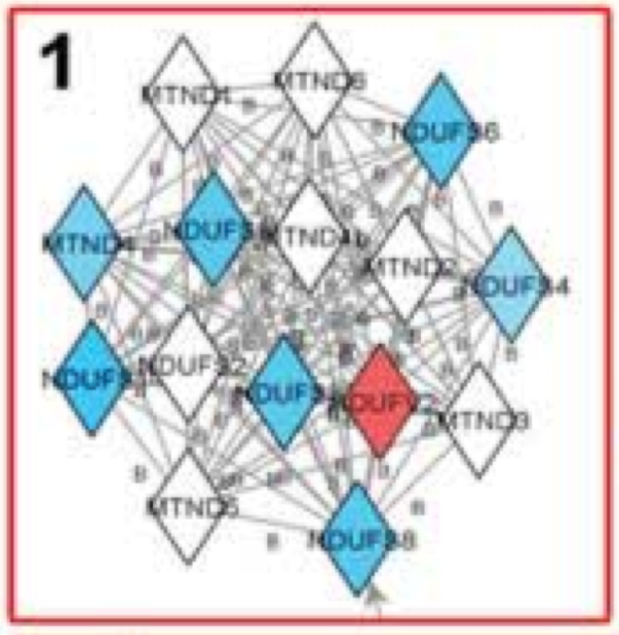
Most eukaryotic cells contain mitochondria, which produce ATP from products of the Krebs cycle, fatty acid oxidation, and amino acid oxidation. At the mitochondrial inner membrane, electrons from NADH and succinate pass through the electron transport chain to oxygen, which is reduced to water. The electron transport chain comprises an enzymatic series of electron donors and acceptors. Each electron donor passes electrons to a more electronegative acceptor, which in turn donates these electrons to another acceptor, a process that continues down the series until electrons are passed to oxygen, the most electronegative and terminal electron acceptor in the chain. Passage of electrons between donor and acceptor releases energy, which is used to generate a proton gradient across the mitochondrial membrane by actively pumping protons into the intermembrane space, producing a thermodynamic state that has the potential to do work.

Energy obtained through the transfer of electrons (black arrows) down the ETC is used to pump protons (red arrows) from the mitochondrial matrix into the intermembrane space, creating an electrochemical proton gradient across the mitochondrial inner membrane (IMM) called ". This electrochemical proton gradient allows ATP synthase (ATP-ase) to use the flow of H^+ through the enzyme back into the matrix to generate ATP from adenosine diphosphate (ADP) and inorganic phosphate.

5. Analysis of the dynamics of inflammation pathways

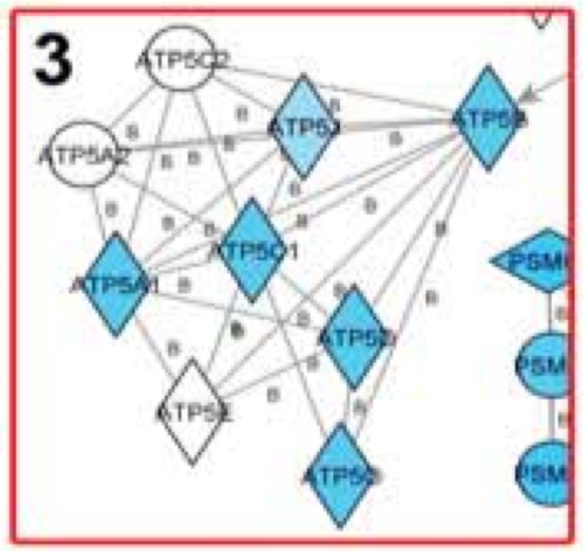
Pathways which are suppressed after LPS treatment

Reduction of modules involved in cell respiration

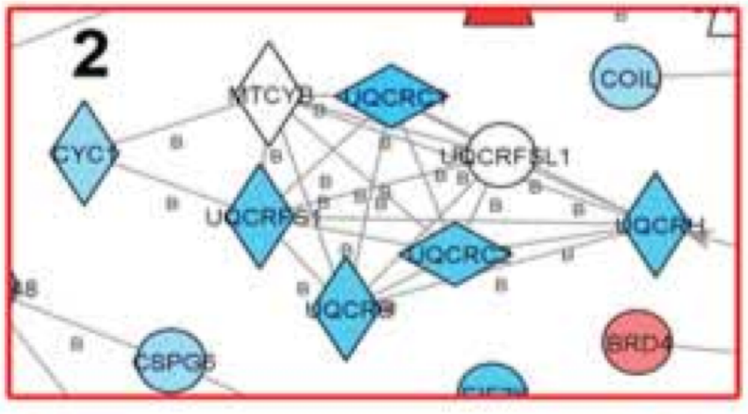


Group 1
mitochondrial respiratory chain complex I (NDUF genes)

NDUF = NADH Ubiquinone oxidoreductase Fe-S

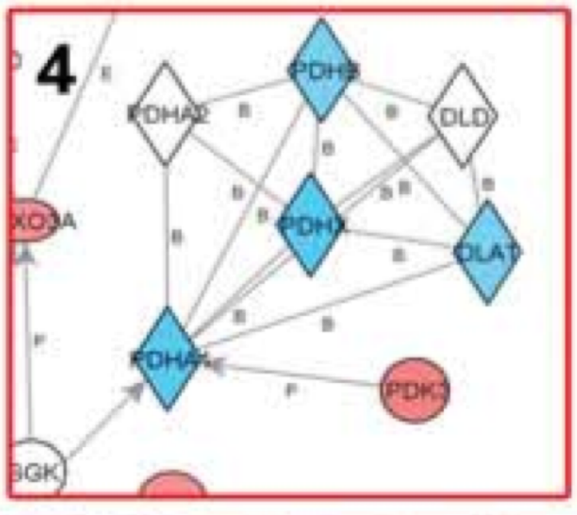


Group 3
ATP synthase complex (ATP5 genes).



Group 2
mitochondrial respiratory chain complex III (UQCR genes).

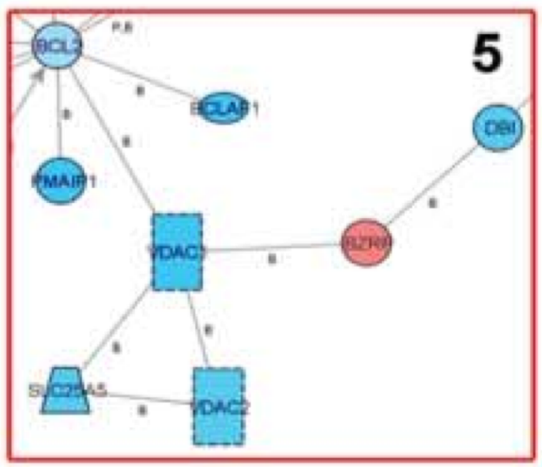
UQCR = ubiquinol-cytochrome c reductase



Group 4
pyruvate dehydrogenase complex.

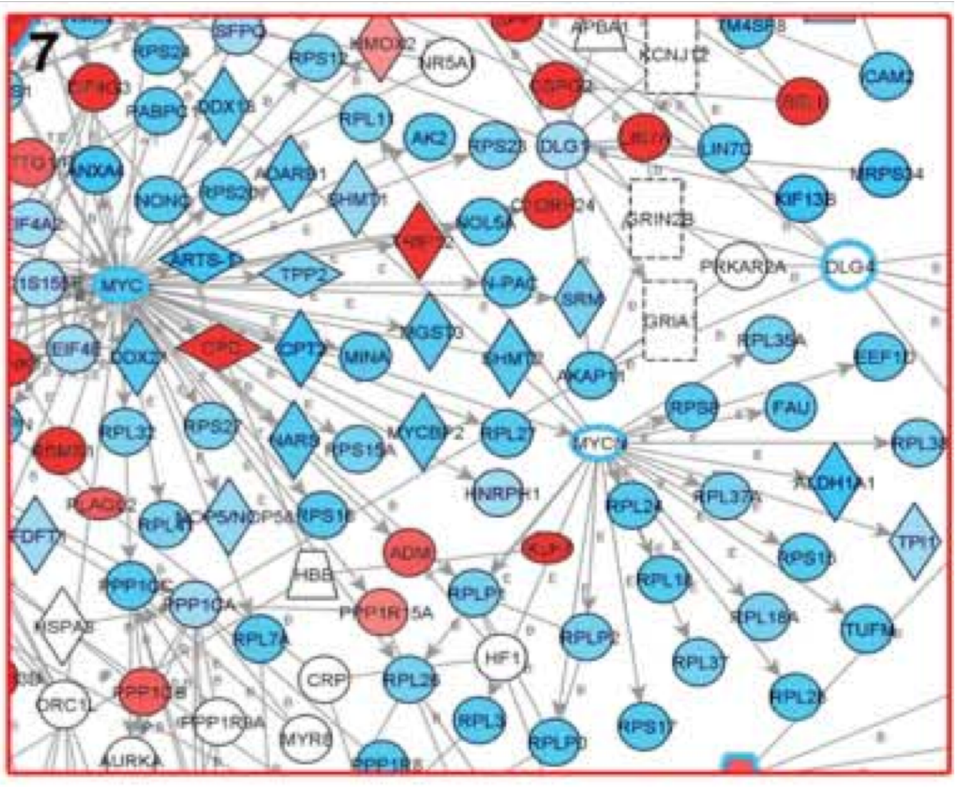
5. Analysis of the dynamics of inflammation pathways

Reduction of genes involved in solute diffusion through mitochondrial membrane

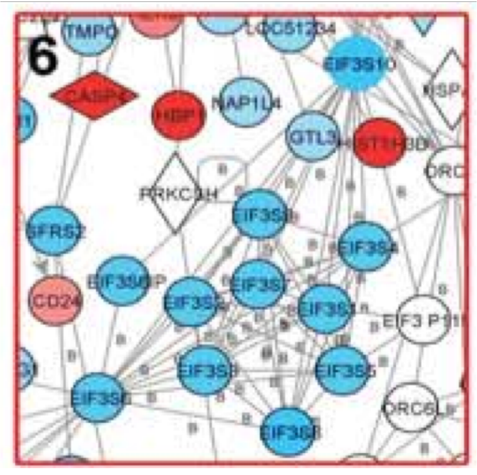


Group 5
mitochondrial permeability transition pore complex

Reduction of modules involved in ribosomial activity



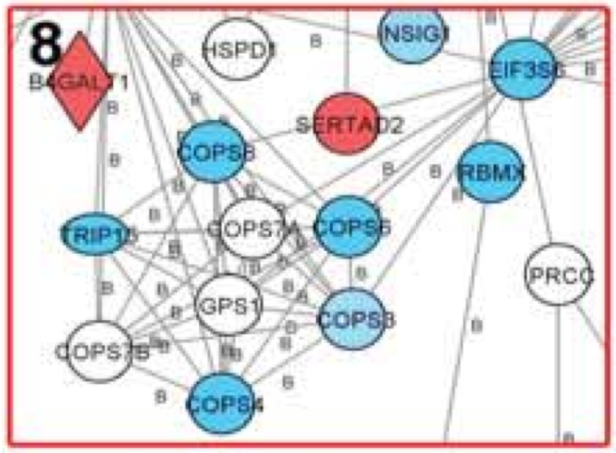
Group 7
ribosomal proteins (RPL, RPS genes).



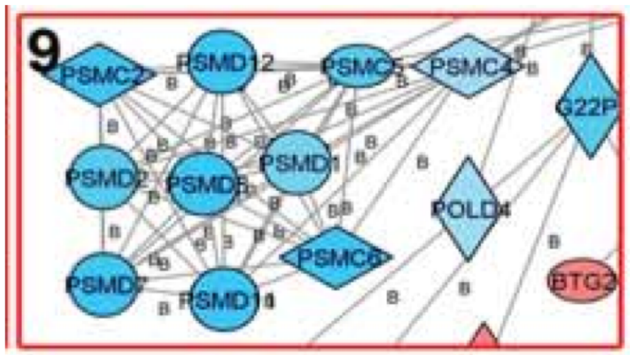
Group 6 Group 6, elongation initiation factor complex (EIF3 genes) importanti nella traslazione.

5. Analysis of the dynamics of inflammation pathways

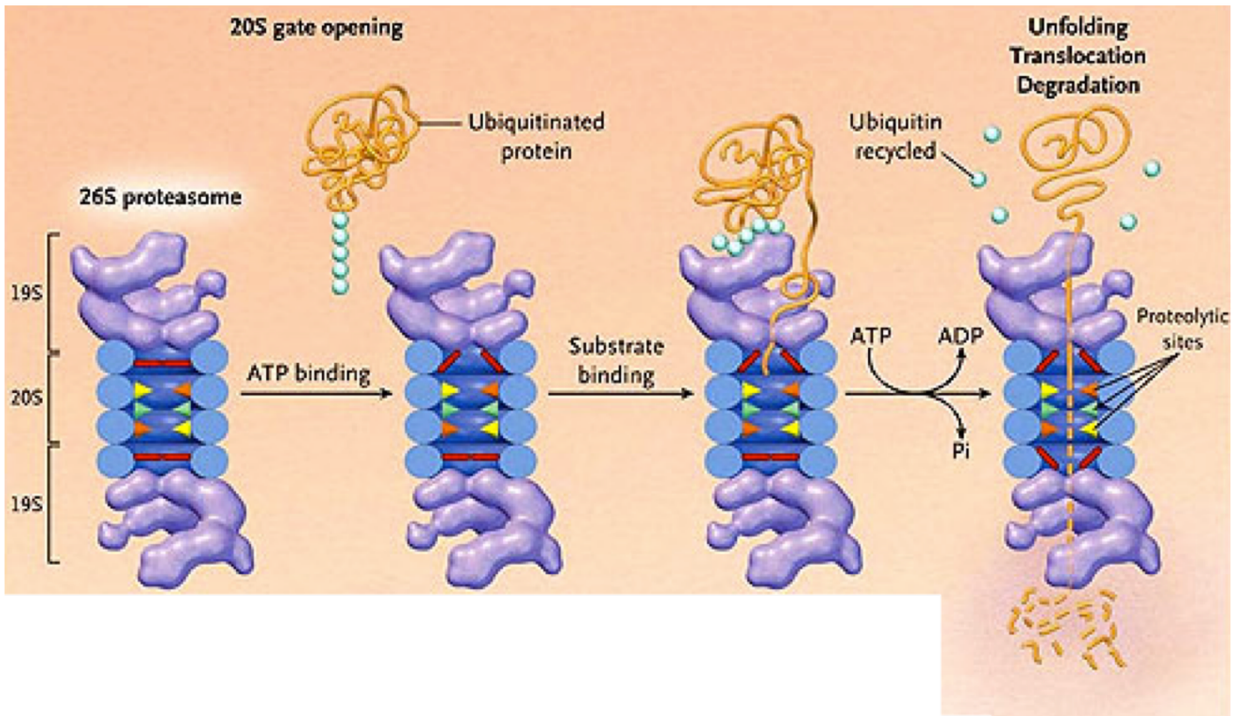
Reduction of modules involved in the ubiquitin-proteasome pathway



Group 8
COP9 signallosome (COPS genes).



Group 9
proteasome (PSM genes).

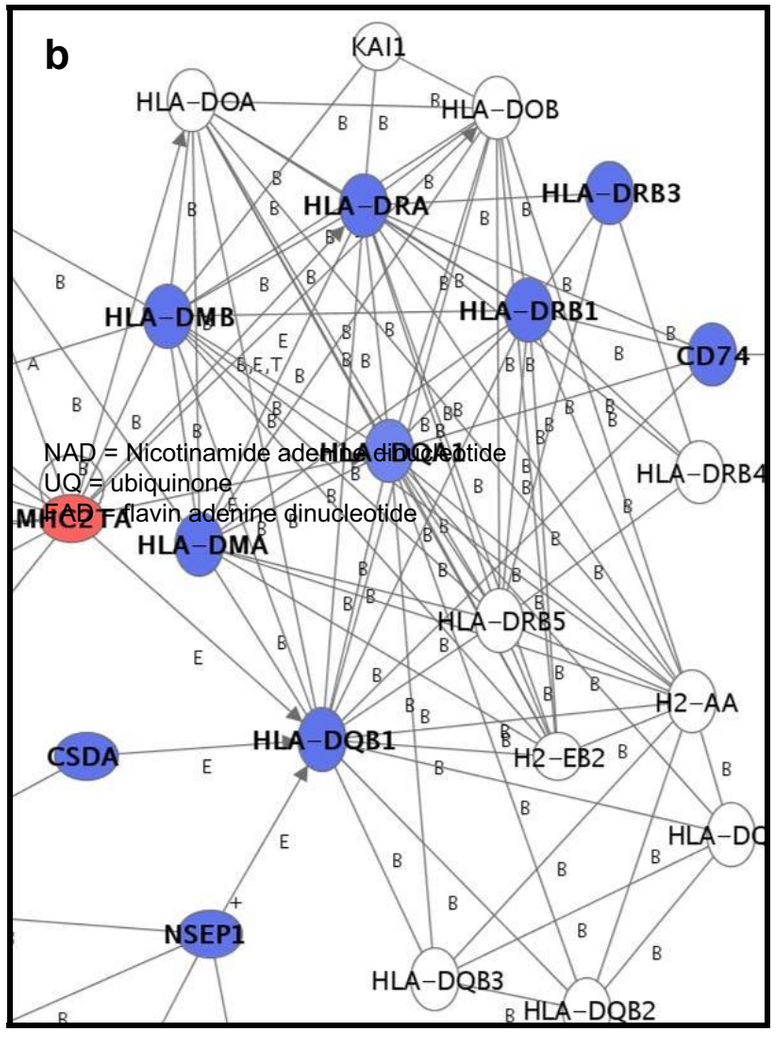


The **ubiquitination system** functions in a wide variety of cellular processes, including:

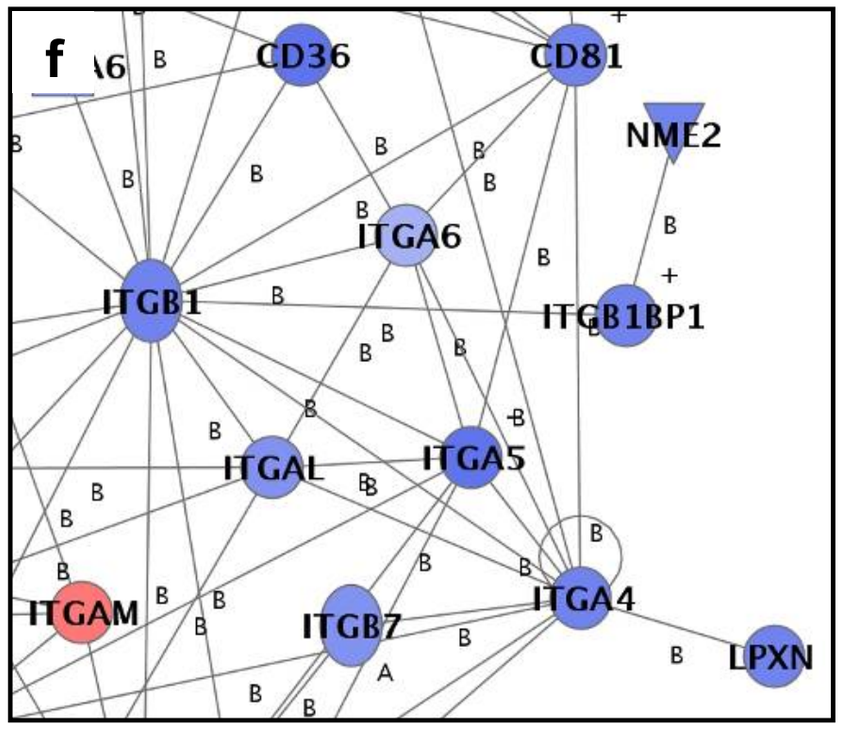
Antigen processing
Apoptosis
Biogenesis of organelles
Cell cycle and division
DNA transcription and repair
Differentiation and development
Immune response and inflammation
Neural and muscular degeneration
Morphogenesis of neural networks
Modulation of cell surface receptors, ion channels and the secretory pathway
Response to stress and extracellular modulators
Ribosome biogenesis
Viral infection

5. Analysis of the dynamics of inflammation pathways

Reduction of genes involved in antigen presentation and leukocyte migration (integrins)

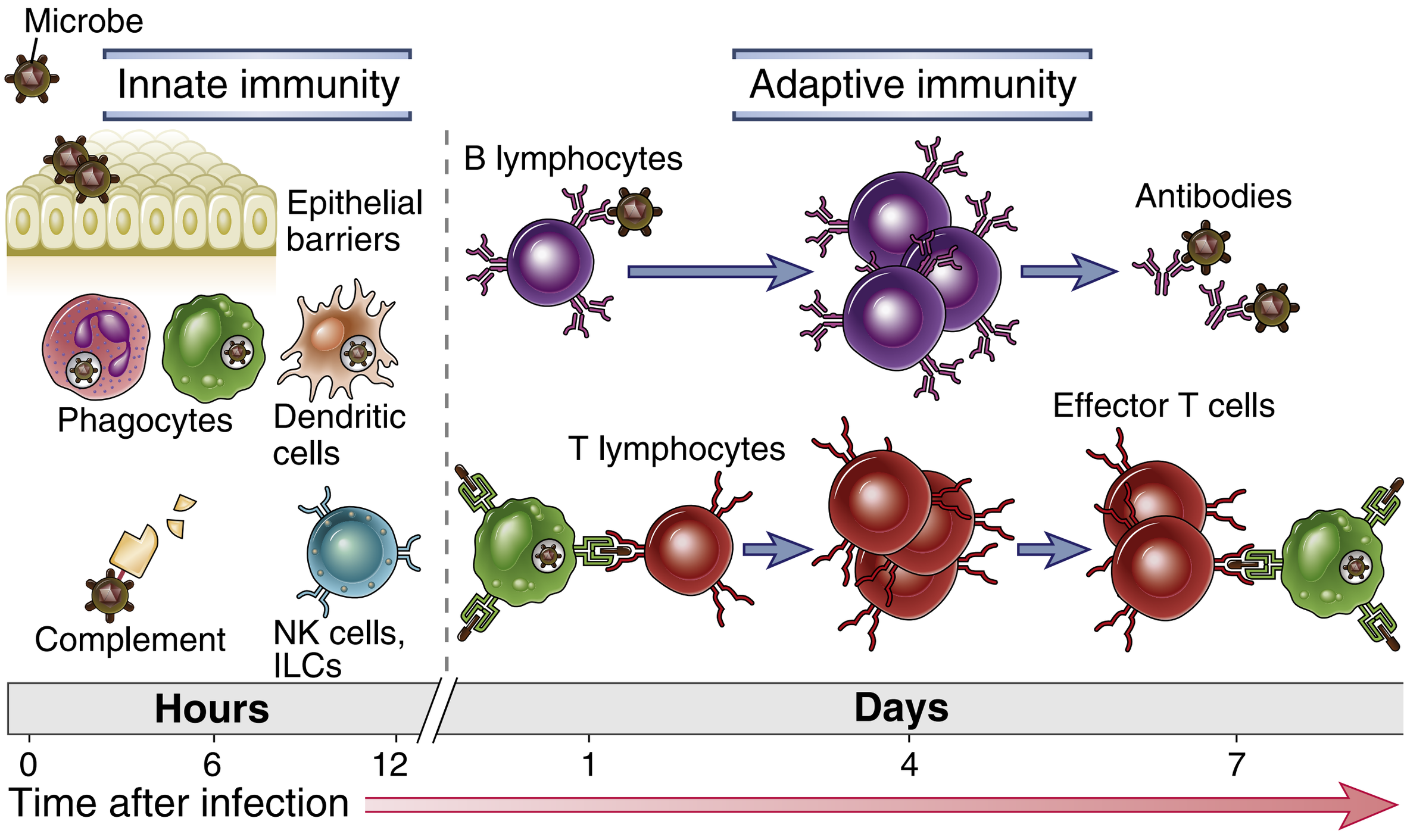


Group a
members of the MHC II complex



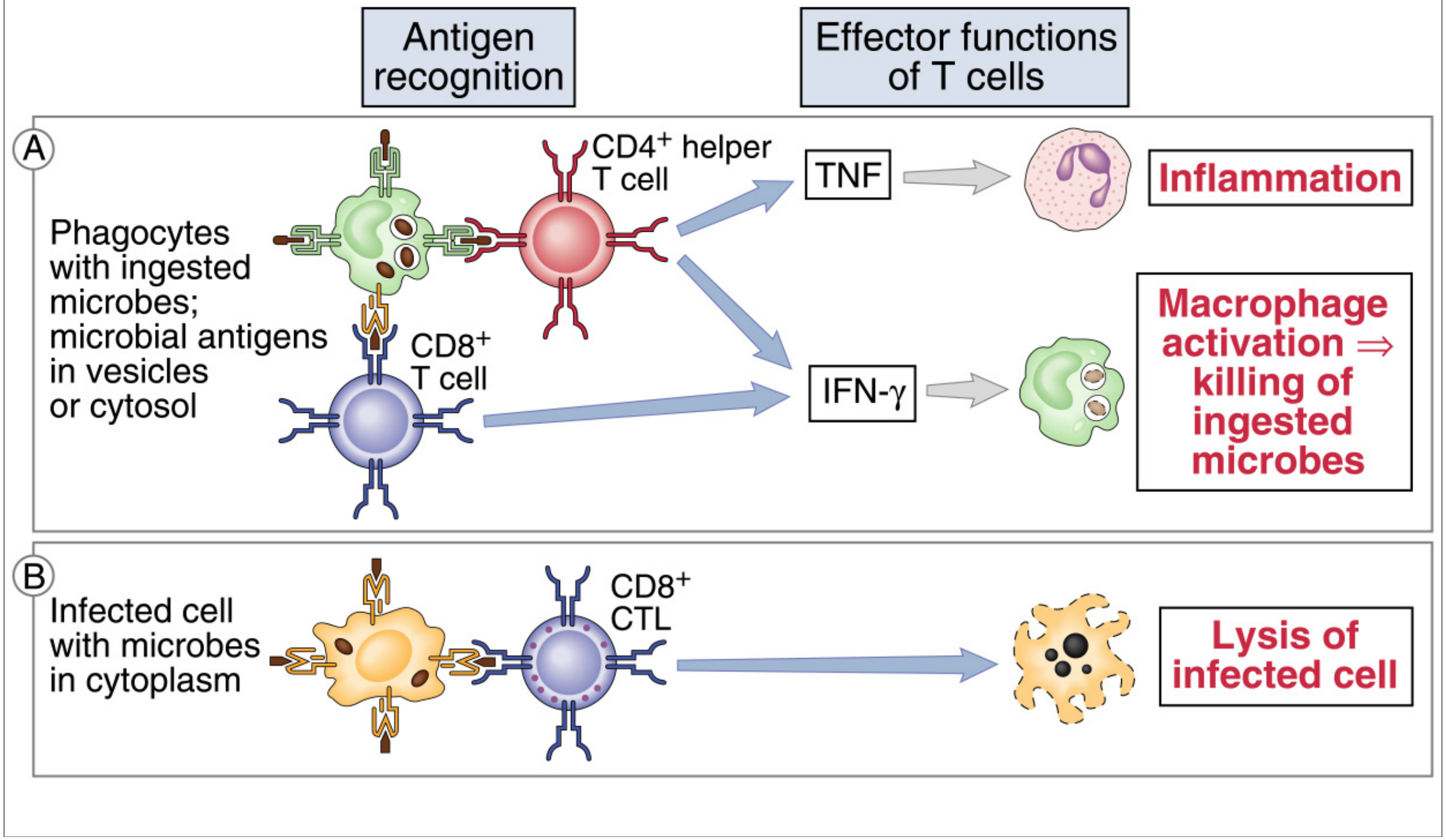
Group f
Integrin chains

Innate and adaptive immunity

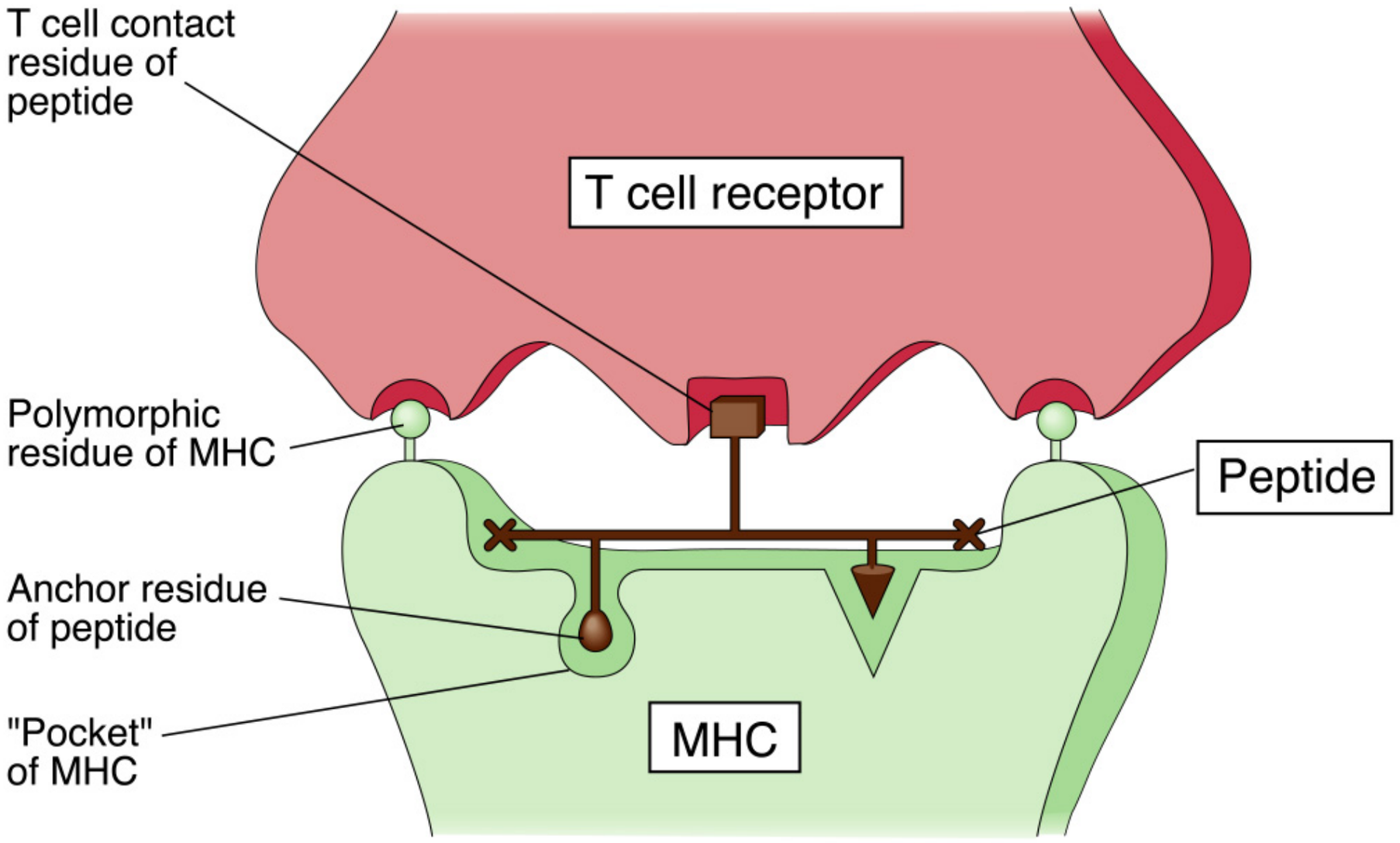


ILC, innate lymphoid cell; *NK,* natural killer.

Cell-mediated immunity



T Cell recognition of a peptide-MHC complex



6. Conclusions on the dynamics of transient systemic inflammatory response

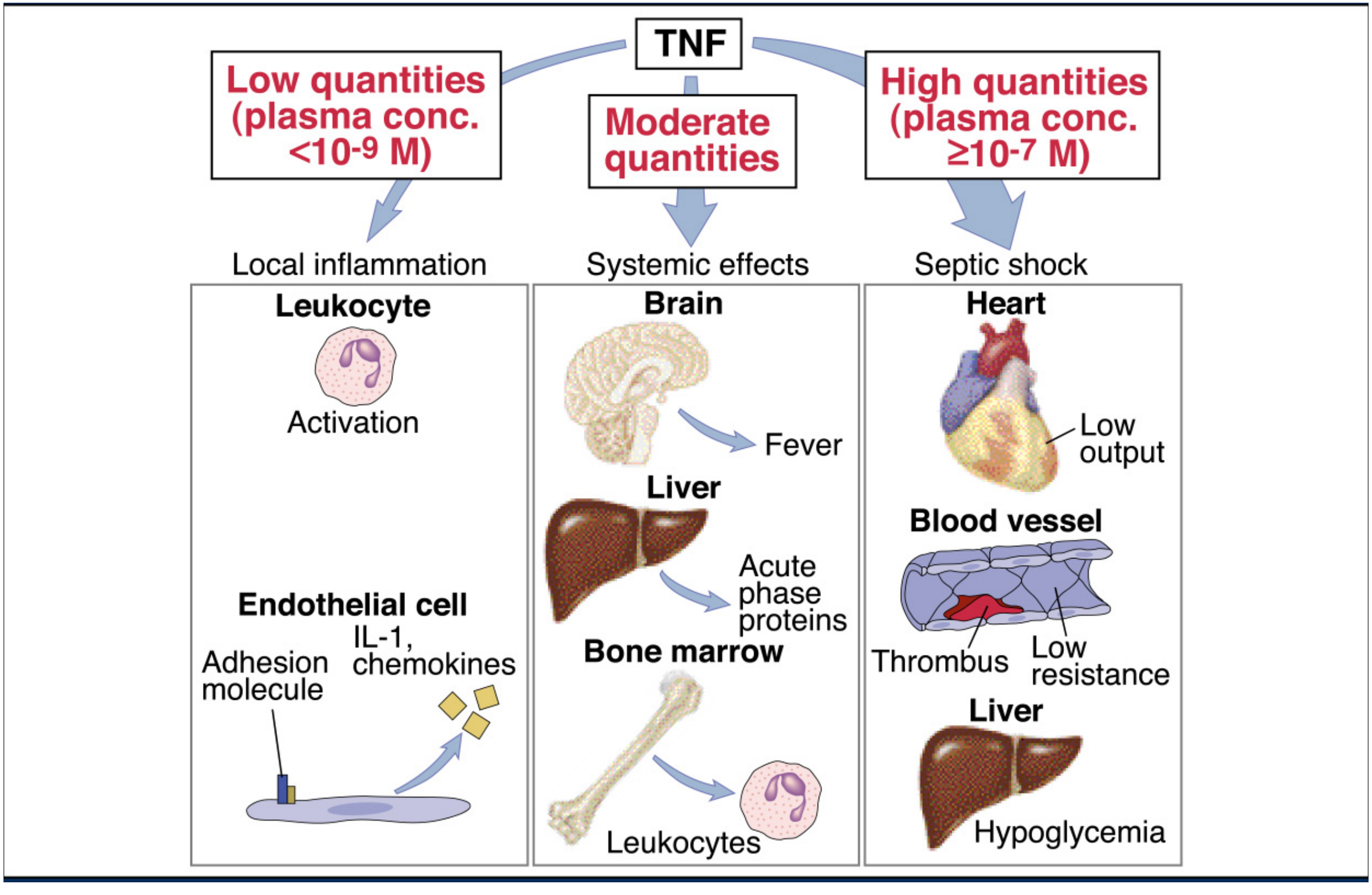
1. The analysis of “virtual cell” shows an early transient increase of gene expression for pro-inflammatory molecules (cytokines, chemokines, ROS, transcription factors, TLRs). At longer time points are expressed genes with anti-inflammatory

2. The analysis of the systemic inflammation network shows dysregulation of modules involved in leukocyte functions : energy metabolism, protein synthesis, protein degradation following transient endotoxemia

3. The suppression of important functional modules suggests that leukocytes exposed to pro-inflammatory stimuli have e reduced capacity to answer to subsequent stimuli (innate immunity tolerance)

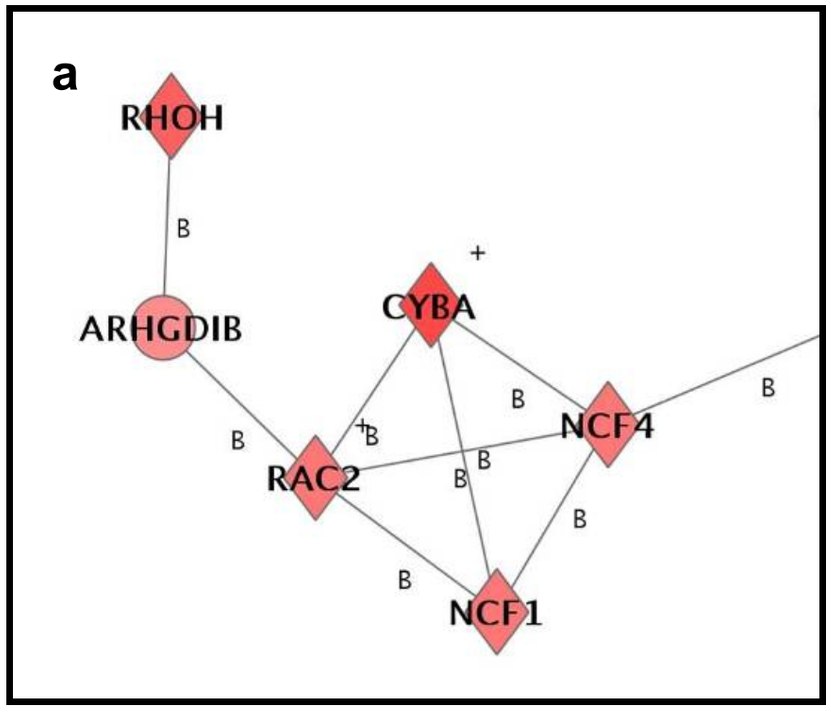
Fine lezione

LPS

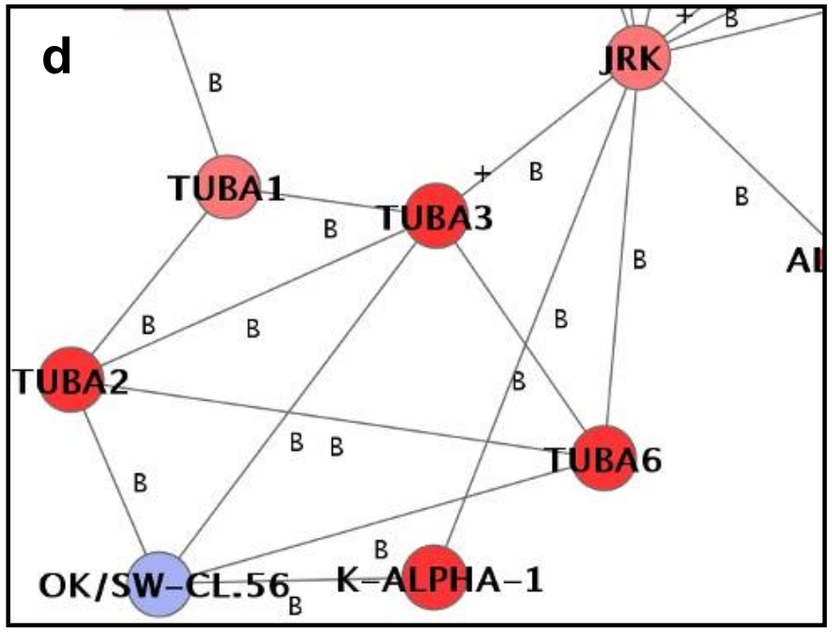

TNF
Low quantities (plasma conc. <10-9 M)
Moderate quantities
High quantities (plasma conc. ≥10-7 M)
Local inflammation
Systemic effects
Septic shock
Leukocyte
Activation
Endothelial cell
IL-1, chemokines
Adhesion molecule
Brain
Fever
Liver
Acute phase proteins
Bone marrow
Leukocytes
Heart
Low output
Blood vessel
Thrombus
Low resistance
Liver
Hypoglycemia

5. Analisi della dinamica delle pathways di geni coinvolti

Attivazione di geni implicati nel danno ossidativo e mitosi



Group a . superoxide-producing phagocyte NADPH-oxidase.



Group d . tubulin-A genes.