DALLA BIOLOGIA DEI PMN

CIRCA IL 50-70% DEL MIDOLLO OSSEO È DEDICATO ALLA PRODUZIONE DEI PMN:
100 MILIARDI DI PMN AL GIORNO!!!
LA MATURAZIONE DEI PMN RICHIÉDE 5 GIORNI!!
LA PERMANENZA NEL SANGUE È DI 10 ORE!!
LA VITA NEI TESSUTI DI 1-2 GIORNI!!
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CHE MODULANO LE FUNZIONI DI MOLTE CELLULE LINFOIDI E NON....

E CHE POSSONO POLARIZZARSI in N1 e N2....
ALLA NUOVA BIOLOGIA DEI MONOCITI/MACROFAGI......

...CON LA LORO NUOVA DIFFERENZAZIONE e POLARIZZAZIONE...

OLD!

NEW!
Macrophages are characterized by high plasticity and integrate different environmental signals leading to different polarized activation profiles.

Macrophage polarization results in a complete reorganization of the transcriptional profile.

Macrophage polarization has profound effects on the macrophage immune settings, with master cytokines and chemokines defining the Th/Mφ network which orient the adaptive immune response.

Macrophage polarization has profound effects on the macrophage metabolic settings, with M1 contributing bactericidal/bacteriostatic activity via iron retention and M2 contributing resolution and tissue repair via iron release.
…ALLA FAGOCITOSI CHE ESPPLICANO!
...ALLA FAGOCITOSI CHE ESPLICANO!

FAGOCITOSI DEI PMN!
...ALLA FAGOCITOSI CHE ESPPLICANO!

FAGOCITOSI DEI PMN!

Trichomonas vaginalis
Confronted by a foe much larger than themselves, neutrophils will "mob" and dismember the invader
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MACROPHAGE:
Another white blood cell
responsible for killing
microbes is ingesting the
yeast Candida albicans

FAGOCITOSI DEI MONOCITI/MACROFAGI!
BIOLOGIA DELLA FAGOCITOSI!

Prof. Ordinario di Patologia e Fisiopatologia Generale ed Immunologia ed Immunopatologia

Dipartimento di Medicina Sperimentale e Patologia
Università degli Studi "La Sapienza"
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00161 Roma
fabrizio.mainiero@uniroma1.it

Il materiale presente in questo documento viene distribuito solamente per uso interno ed esclusivamente a scopo didattico.
BIOLOGIA DELLA FAGOCITOSI!

Nuovi meccanismi extra-fagocitici: la NECTOSI!

Prof. Fabrizio Mainiero

Prof. Ordinario di Patologia e Fisiopatologia Generale ed Immunologia ed Immunopatologia

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Endocytosis
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Endocytosis is the actin-independent process by which all cells internalize small molecules. There are various mechanisms of endocytosis, including internalization into clathrin-coated pits, which are roughly 100 nm in diameter and which concentrate receptors and other surface molecules into early endosomes.

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This process of 'cell drinking' involves the eruption of membrane ruffles from the cell surface that subsequently collapse back and fuse with the plasma membrane to engulf surrounding liquid. Newly formed macropinosomes (which are typically 0.5–5 µm in diameter) contract and fuse with compartments of the normal endocytic pathway. This process requires extensive actin mobilization. All cells engage in macropinocytosis.
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Sometimes cells actively 'eat' other healthy live cells (for example, tumour cells can 'eat' lymphocytes). The target cell is typically killed and degraded.
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La fagocitosi è tra le principali funzioni delle cellule infiammatorie/immunitarie!

<table>
<thead>
<tr>
<th>Monocytes</th>
<th>Activated function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrophage</td>
<td>Phagocytosis and activation of bactericidal mechanisms</td>
</tr>
<tr>
<td>Dendritic cell</td>
<td>Antigen uptake in peripheral sites</td>
</tr>
<tr>
<td>Neutrophil</td>
<td>Phagocytosis and activation of bactericidal mechanisms</td>
</tr>
<tr>
<td>Eosinophil</td>
<td>Killing of antibody-coated parasites</td>
</tr>
<tr>
<td>Basophil</td>
<td>Release of histamine</td>
</tr>
<tr>
<td>Mast cell</td>
<td>Release of granules containing histamine and other active agents</td>
</tr>
</tbody>
</table>

Figure 1-4 Immunobiology, 6/e. (© Garland Science 2005)
LA FAGOCITOSI È STATA SCOPERTA DA
Llyya METCHNIKOFF
ALLA FINE DEL 19th SECOLO!!!!!!

1° LAVORO SULLA FAGOCITOSI:
Metchnikoff, Immunity in the Infectious Diseases,

SONO PASSATI PIÙ DI 100 ANNI DALLA SCOPERTA DELLA BIOLOGIA DELLA FAGOCITOSI!!!!!!!
LA FAGOCITOSI ELIMINA CELLULE MORTE, come quelle necrotiche o apoptotiche, O DESTINATE A MORIRE, come i patogeni o le cellule tumorali, coperte da sostanze opsoniniche e riconosciute da recettori fagocitici!
LA FAGOCITOSI ELIMINA CELLULE MORTE, come quelle necrotiche o apoptotiche, O DESTINATE A MORIRE, come i patogeni o le cellule tumorali, coperte da sostanze opsoniniche e riconosciute da recettori fagocitici! LA FAGOCITOSI CLASSICA!
This term is created by combining phago-, which is derived from the ancient Greek ‘phagein’ meaning to devour, and -ptosis, which is from the ancient Greek ‘ptosis’ meaning to fall; used here with the connotation of dying; therefore, phagoptosis would connote ‘devouring-induced death’ or ‘death caused by being devoured’.

RECENTEMENTE SI È DIMOSTRATO CHE LA FAGOCITOSI ELIMINA ANCHE CELLULE VIVE!

La **phagoptosis**!
Eaten alive! Cell death by primary phagocytosis: 'phagoptosis'.

Brown GC, Neher JJ.

Phagoptosis, also called primary phagocytosis, is a recently recognised form of cell death caused by phagocytosis of viable cells, resulting in their destruction. It is provoked by exposure of 'eat-me' signals and/or loss of 'don't-eat-me' signals by viable cells, causing their phagocytosis by phagocytes. Phagoptosis mediates turnover of erythrocytes, neutrophils and other cells, and thus is quantitatively one of the main forms of cell death in the body. It defends against pathogens and regulates inflammation and immunity. However, recent results indicate that inflamed microglia eat viable brain neurons in models of neurodegeneration, and cancer cells can evade phagocytosis by expressing a 'don't-eat-me' signal, suggesting that too much or too little phagoptosis can contribute to pathology. This review provides an overview of the molecular signals that regulate phagoptosis and the physiological and pathological circumstances in which it has been observed.
As a result of activation or stress, cells can expose a variety of ‘eat-me’ signals, including: calreticulin (CRT), thrombospondin 1 (TSP1), complement factors C3b and C1q, and phosphatidylserine (PS). CRT and TSP1 activate phagocytosis via lipoprotein receptor-related protein (LRP). C3b and C1q activate via complement receptors (CRs), and phosphatidylserine activates either via directly binding receptors such as stabilin, Tim (T-cell immunoglobulin-and mucin-domain-containing molecule) and BAI or via binding adaptor proteins such as Gas6 (Growth arrest-specific 6) and MFG-E8 (milk fat globule EGF-like factor-8), which activate phagocytosis via Mer tyrosine kinase (MerTK) and the vitronectin receptor (VR), respectively.
The Two-Step Engulfment of Apoptotic Cells. In the tethering step, the phosphatidylserine (PtdSer) receptor Tim4 tightly binds PtdSer on the apoptotic cell and recruits it to the macrophage surface. In the tickling or uptake step, soluble proteins such as protein S/Gas6 or MFG-E8 bind PtdSer on apoptotic cells and activate their receptors (MerTK or integrin, respectively) on phagocytes, leading to Rac1 activation and actin polymerization. Both tethering and tickling are essential steps in the efficient engulfment of apoptotic cells in mouse-resident peritoneal macrophages. Whether a similar two-step engulfment mechanism that occurs in the engulfment of apoptotic cells in other macrophages remains to be studied. Abbreviations: Gas6, growth arrest-specific 6; MFG-E8, milk fat globule EGF factor 8.
The seven-transmembrane receptor BAI1 directly binds the PtdSer on the surface of an apoptotic cell, which results in the recruitment of the ELMO-DOCK ('engulfment and cell motility–downstream of Crk') complex, which functions as a guanine-exchange factor for the small GTPase Rac. The activation of Rac promotes remodeling of the actin cytoskeleton required for engulfment of the apoptotic cellular 'corpse'. Integrins αVβ3 or αVβ5 and members of the TAM family of receptors bind apoptotic cells indirectly, via PtdSer-bound bridging molecules MFG-E8, Gas-6 or protein S, which results in activation of the kinase FAK and contributes to the activation of Rac1.

Phagocytosis of apoptotic cells in homeostasis.
Arandjelovic S, Ravichandran KS.
The complex ‘Eat-me’ signalling!

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The complex ‘Eat-me’ signalling!
The 'eat-me' signals are recognized by different engulfment receptors on the phagocytes, which results in signaling events that facilitate uptake of the apoptotic cellular 'corpse'. Engulfment also elicits transcriptional upregulation of the cholesterol-efflux transporter ABCA1 and increased expression of engulfment receptors. Within the mitochondria, the levels of the uncoupling protein UCP2 are increased, which enables the continued uptake of apoptotic cellular 'corpses'. Anti-inflammatory mediators are expressed and secreted, which contributes to tissue homeostasis and inhibition of local inflammation. CX3CR, chemokine CX3CL1 receptor; G2A, G protein–coupled receptor; S1P1, sphingosine 1-phosphate (S1P) receptor; LPC, lysophosphatidylcholine; RAGE, receptor for advanced glycation end products; LRP1, low-density lipoprotein receptor–related protein; TSP1, thrombospondin; CRT, calreticulin.
Cells can expose ‘don’t-eat-me’ signals to block their phagocytosis, including: CD47, which binds phagocyte SIRPα (signal-regulatory protein α); and sialic acid residues, which block phagocytosis by binding phagocyte siglec (sialic acid binding Ig-like lectin) and preventing binding of the ‘eat-me’ signals complement C1q and C3b. Cells can lose these ‘don’t-eat-me’ signals when aged, stressed or infected.
Phagoptosis mediates turnover of erythrocytes, neutrophils and other cells, and thus is quantitatively one of the main forms of cell death in the body!

Table I. Rough estimates of the physiological rates of cell turnover by different forms of cell death in humans

<table>
<thead>
<tr>
<th>Type of cell death</th>
<th>Cells</th>
<th>Rate (thousands of cells/second)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phagoptosis</td>
<td>Erythrocytes Neutrophils</td>
<td>2000 500–1000</td>
</tr>
<tr>
<td>Shedding</td>
<td>Enterocytes</td>
<td>80</td>
</tr>
<tr>
<td>Cornification</td>
<td>Keratinocytes</td>
<td>40</td>
</tr>
<tr>
<td>Necrosis</td>
<td>Enterocytes</td>
<td>10</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>T cells and B cells</td>
<td>1</td>
</tr>
<tr>
<td>Autophagy</td>
<td>None known</td>
<td></td>
</tr>
</tbody>
</table>
Increasing levels of cellular stress or insult can cause: adaptation, phagoptosis, apoptosis and necrosis.

Phagoptosis is a recently recognised form of cell death!
NEW! Phagoptosis: Homeostatic clearance of apoptotic cells via different phagocytes!
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In many tissues of the body, clearance of apoptotic cells is performed by the professional phagocytes (P), among which are neutrophils, tissue-resident macrophages and immature dendritic cells.
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• professional phagocytes (P),
• non professional phagocytes (NP),
• specialized phagocytes (SP)
LA FAGOCITOSI CLASSICA:
ELIMINAZIONE DI CELLULE MORTE, come quelle necrotiche o apoptotiche, O DESTINATE A MORIRE, riconosciute da recettori fagocitici o coperte da sostanze opsoniniche, come i patogeni o le cellule tumorali!
LA FAGOCITOSI PUÒ ESSERE DIRETTA O INDIRETTA!

The binding of pathogen to the macrophage can be direct or indirect.
LA FAGOCITOSI SI PUÒ DIVIDERE IN BASE AI RECETTORI COINVOLTI ED ALLE MOLECOLE CONVOLTE IN:

NON OPSONINICA ed OPSONINICA

LA FAGOCITOSI NON OPSONINICA È MEDIATA DA:

• Recettori per il mannoso e lectinici (es. dectina)
• Recettori Toll *(triggered non-specific phagocytosis)*
• Recettori spazzino (Scavenger) (es. MARCO)
• Recettori integrinici (es. Integra alfa5b5)
• Le opsonine non classiche sono tutti i ligandi dei suddetti recettori componenti o adesi alla parete: mannosio, MBL, LBP, AGE, trombospondina etc.

LA FAGOCITOSI OPSONINICA È MEDIATA DA:

• Recettori per il complemento e frammenti di questo
• Recettori per il frammento cristallizzabile degli anticorpi e quest’ultimi
• Recettori integrinici (es. Integra alfa5b1) e la fibronectina
• Le opsonine classiche sono gli anticorpi, frammenti del complemento (C3B, C4b, etc.) e fibronectina
**Selected receptors involved in phagocytosis!!!**


**Information processing during phagocytosis.**

Underhill DM, Goodridge HS.

Inflammatory Bowel & Immunobiology Research Institute, Department of Biomedical Sciences, Cedars-Sinai Medical Center, 8,700 Beverly Boulevard, Los Angeles, California 90048, USA. David.Underhill@csmc.edu

<table>
<thead>
<tr>
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<th>Receptors</th>
<th>Ligands</th>
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<tbody>
<tr>
<td>Opsonic phagocytosis</td>
<td>Fc receptor family (FcyRI, FcyRIIA and FcyRIIA)</td>
<td>Antibody-opsonized targets</td>
</tr>
<tr>
<td></td>
<td>Complement receptors (CR1, CR3 and CR4)</td>
<td>Complement-opsonized targets</td>
</tr>
<tr>
<td></td>
<td>a5β1 integrin</td>
<td>Fibronectin</td>
</tr>
<tr>
<td>Non-opsonic phagocytosis</td>
<td>Dectin 1</td>
<td>β-glucan</td>
</tr>
<tr>
<td></td>
<td>Macrophage receptor MARCO</td>
<td>Bacteria (undefined specific ligand)</td>
</tr>
<tr>
<td></td>
<td>Scavenger receptor A</td>
<td>Bacteria (diverse charged molecules)</td>
</tr>
<tr>
<td></td>
<td>aVβ5 integrin</td>
<td>Apoptotic cells</td>
</tr>
<tr>
<td>Triggered (nonspecific) phagocytosis</td>
<td>Toll-like receptors</td>
<td>Various, including lipopolysaccharides and lipopeptides</td>
</tr>
<tr>
<td></td>
<td>FcyR, Fc receptor for IgG</td>
<td></td>
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</tbody>
</table>
LA FAGOCITOSI NON OPSONINICA È MEDIATA DAI RECETTORI NON OPSONINICI CLASSICI E LORO LIGANDI!

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Le opsonine non classiche sono tutti i ligandi dei suddetti recettori componenti della o adesi alla parete:

- mannosio,
- MBL,
- LBP,
- AGE,
- trombospondina
- etc.
I Recettori Toll MEDIANO la “triggered non-specific phagocytosis”!
LA FAGOCITOSI OPSONINICA È MEDIATA DAI RECETTORI OPSONINICI CLASSICI!

Receptors for **OPSONINS**:  
- CR1, CR3, and CR4 (for C3b, iC3b)  
- Fc\(\gamma\)RI, IIA, and III (for IgG)  
- Recettori integrinici (es. Integrina alfa5b1) e la fibronectina
LA FAGOCITOSI OPSONINICA È MEDIATA DAI RECETTORI OPSONINICI CLASSICI!

Receptors for **OPSONINS**: 
- CR1, CR3, and CR4 (for C3b, iC3b)
- Fc\(_\gamma\)RI, IIA, and III (for IgG)
- Recettori integrinici (es. Integrina alfa5b1) e la fibronectina
Acting and inhibitory FcγR control phagocytosis of IgG-opsonized particles!

IgG opsonized particle

activin polymerization and particle internalization

FcγRII, FcγRI, FcγRIII

Src family

phosphorylation of ITAMs

Syk

Activating and inhibitory FcγR control phagocytosis of IgG-opsonized particles!
I classici recettori per le osponine del Complemento!

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Specificity</th>
<th>Functions</th>
<th>Cell types</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1 (CD35)</td>
<td>C3b, C4b iC3b</td>
<td>Promotes C3b and C4b decay, Stimulates phagocytosis, Erythrocyte transport of immune complexes</td>
<td>Erythrocytes, macrophages, monocytes, polymorphonuclear leukocytes, B cells, FDC</td>
</tr>
<tr>
<td>CR2 (CD21)</td>
<td>C3d, iC3b, C3dg Epstein–Barr virus</td>
<td>Part of B-cell co-receptor, Epstein–Barr virus receptor</td>
<td>B cells, FDC</td>
</tr>
<tr>
<td>CR3 (Mac-1) (CD11b/CD18)</td>
<td>iC3b</td>
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<td>Macrophages, monocytes, polymorphonuclear leukocytes, FDC</td>
</tr>
<tr>
<td>CR4 (gp150,95) (CD11c/CD18)</td>
<td>iC3b</td>
<td>Stimulates phagocytosis</td>
<td>Macrophages, monocytes, polymorphonuclear leukocytes, dendritic cells</td>
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</table>

I Recettori per i frammenti C3b (e suoi derivati) e C4b mediano l’opsonizzazione e la fagocitosi!!!

**Fissazione del complemento!**
I classici recettori per le osponentine del Complemento!

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Diagram:
- **Opsonization**
  - Complement
  - Bacterium
  - CR
- **Binding**
  - C3b
  - iC3b
  - C4b
- **Phagocytosis**
  - CR
  - Phagocytic cell
I classici recettori per le osponine del Complemento!

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**Diagram:**
- Opsonization
- Binding
- Phagocytosis

- Complement: C3b, iC3b, C4b
- Bacterium
- CR
- Phagocytic cell
I RECETTORI OPSONINICI E NON SVOLGONO RUOLI DIVERSI DURANTE LA FAGOCITOSI!
I RECETTORI OPSONINICI E NON DURANTE LA FAGOCITOSI CONTROLLANO:
IRECETTORI OPSONINICI E NON DURANTE LA FAGOCITOSI CONTROLLANO:
I RECETTORI OPSONINICI E NON DURANTE LA FAGOCITOSI CONTROLLANO:
I RECETTORI OPSONINICI E NON DURANTE LA FAGOCITOSI CONTROLLANO:

SENSING!
I RECETTORI OPSONINICI E NON DURANTE LA FAGOCITOSI CONTROLLANO:

SENSING!
SENSING!
(TASTING and FEELING)!

I RECETTORI OPSONINICI E NON DURANTE LA FAGOCITOSI CONTROLLANO:
I RECETTORI OPSONINICI E NON DURANTE LA FAGOCITOSI CONTROLLANO:

SENSING!

(TASTING and FEELING)!
SENSING!
(TASTING and FEELING)!
SWALLOWING!
I RECETTORI OPSONINICI E NON DURANTE LA FAGOCITOSI CONTROLLANO:

SENSING!

(TASTING and FEELING)!

SWALLOWING!
SENSING!

(TASTING and FEELING)!

SWALLOWING!

DIGESTING!
As phagocytosis proceeds from the initial binding of a target to actin-dependent internalization and ultimately to degradation of the target in the phagolysosome, myeloid cells acquire information about the target through a variety of mechanisms. At the cell surface, receptors sample the chemical constituents of the particle and membrane dynamics facilitate an assessment of its physical properties. Additional information is gathered as the phagosome pinches off from the plasma membrane and as it matures through interactions with other intracellular compartments. Finally, the degradation of the target exposes ligands that were not previously accessible and releases ligands into the cytosol for detection by intracellular receptors. The information gathered by all of these processes is integrated to shape the ensuing immune response.
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Information processing at different stages of phagocytosis!

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Nature Reviews Immunology 12, 492-502 (July 2012)
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Lo SWALLOWING e il DIGESTING corrispondono all'endocitosi e formazione del fagolisosoma!

- Induzione di protrusioni di membrana chiamate pseudopodi che avvolgono il microbo
- Fusione degli pseudopodi permette l'inglobamento del microbo in una struttura chiamata fagosoma
- Fusione del fagosoma con il lisosoma e formazione di un fagolisosoma
- Il contenuto digerito viene eliminato mediante un processo di esocitosi
LA DINAMICITÀ DELLA FAGOCITOSI!

PHAGOCYTOSIS: To defend the body against bacteria, human neutrophils (white blood cells) ingest invading pathogens like this *E. coli*. 
LA DINAMICITÀ DELLA FAGOCITOSI!

PHAGOCYTOSIS: To defend the body against bacteria, human neutrophils (white blood cells) ingest invading pathogens like this *E. coli*.
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LA DINAMICITÀ DELLA FAGOCITOSI!

PHAGOCYTOSIS: Sensing Swallowing
To defend the body against bacteria, human neutrophils (white blood cells) ingest invading pathogens like this E. coli.
LA DINAMICITÀ DELLA FAGOCITOSI!

PHAGOCYTOSIS:
To defend the body against bacteria, human neutrophils (white blood cells) ingest invading pathogens like this *E. coli*.
I RECEPTORI OPSONINICI E NON DURANTE LA FAGOCITOSI STABILISCONO UN'INTERAZIONE SINAPTICA TRA FAGOCITA E TARGET FAGOCITICO:

LA SINAPSIS FAGOCITICA!
The Phagocytic Synapse!

Sequential Recognition and engulfment of *E. coli* is initially mediated by high-affinity, low-specificity interaction with LBP and the scavenger receptors, CD14, and SRA. These molecules then recruit regulators of the cytoskeleton such as integrin β2 to trigger engulfment. In addition, reorganization within the plasma membrane delivers LPS to lower affinity but high-specificity molecules (MD2 and TLR4) to initiate signaling. Signaling occurs either at the cell surface or within the phagosome.
The Phagocytic Synapse resembles the T-DC synapse!

The membrane reorganization events during recognition of *E. coli* may bear similarities to the T cell synapse.

- The T cell synapse is characterized by an initial high-affinity, low-specificity interaction LFA-1/ICAM-1 that mediates noncognate attachment.

- Similar events may occur within the phagocytic synapse in which the low-specificity but high-affinity recognition by scavenger receptors and integrins initiate binding and then subsequent reorganization both triggers engulfment and delivers LPS and other ligands to their cognate TLR to initiate signaling.
Phagocytic synapse formation permits dectin 1 to distinguish between soluble and particulate β-glucans!!!

Dectin 1 engages both particulate β-glucans and soluble β-glucan polymers, but only particulate β-glucans activate phagocytosis and inflammatory responses. The phosphatases CD45 and CD148 regulate signal transduction by the dectin 1 hemi-immunoreceptor tyrosine-based activation motif (hemITAM) and must be isolated from the clustered receptors by the formation of a synapse to permit productive dectin 1 signalling. Soluble β-glucans bind with high affinity to dectin 1 but do not form synapses and therefore fail to trigger dectin 1-mediated responses. PTP, protein tyrosine phosphatase; ROS, reactive oxygen species.

Nature Reviews Immunology 12, 492-502 (July 2012)
The phagocytosis: an overview!!!
The phagocytosis: an overview!!!
The phagocytosis: an overview!!!
The phagocytosis: an overview!!!

Extension of macrophage pseudopodia during engulfment of an IgG opsonized sheep erythrocyte, by a zipper-type mechanism!
IL DIGESTING NELLA FAGOCITOSI!
IL DIGESTING NELLA FAGOCITOSI!
MECCANISMI E FATTORI COINVOLTI NEL KILLING DEI PATOGENI!
### IL DIGESTING NELLA FAGOCITOSI!

**MECCANISMI E FATTORI COINVOLTI NEL KILLING DEI PATOGENI!**

<table>
<thead>
<tr>
<th>Class of mechanism</th>
<th>Specific products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acidification</td>
<td>pH=3.5–4.0, bacteriostatic or bactericidal</td>
</tr>
<tr>
<td>Toxic oxygen-derived</td>
<td>Superoxide $O_2^-$, hydrogen peroxide $H_2O_2$, singlet oxygen $^1O_2^*$,</td>
</tr>
<tr>
<td>products</td>
<td>hydroxyl radical $OH^-$, hypohalite $OCl^-$</td>
</tr>
<tr>
<td>Toxic nitrogen oxides</td>
<td>Nitric oxide $NO$</td>
</tr>
<tr>
<td>Antimicrobial peptides</td>
<td>Defensins and cationic proteins</td>
</tr>
<tr>
<td>Enzymes</td>
<td>Lysozyme—dissolves cell walls of some Gram-positive bacteria. Acid hydrolases—</td>
</tr>
<tr>
<td></td>
<td>further digest bacteria</td>
</tr>
<tr>
<td>Competitors</td>
<td>Lactoferrin (binds Fe) and vitamin $B_{12}$-binding protein</td>
</tr>
</tbody>
</table>

*Figure 2-6 Immunobiology, 6/e. (© Garland Science 2005)*
I meccanismi microbicidi dei Fagociti:
I Meccanismi microbicidi dei Fagociti:

[Diagram showing the mechanisms of microbicidal action of phagocytes, including the interactions of the fagocytic vacuole, lysosomal enzymes, reactive oxygen species (ROS), and nitric oxide (NO).]
I Meccanismi microbicidi dei Fagociti:

- Ossigeno indipendenti

Diagramma illustrativo dei meccanismi microbicidi dei fagociti, mostrando la produzione di ossidasi fagocitica e intermedi reattivi dell'ossigeno (ROI) e l'uso dell'ossido nitrico (NO) per uccidere i microbi extracellulari.
I Meccanismi microbicidi dei Fagociti:

- Ossigeno indipendenti
- Ossigeno dipendenti
I Meccanismi microbicidi dei Fagociti:

- Ossigeno indipendenti
- Ossigeno dipendenti
- Azoto dipendenti
I Meccanismi microbicidi Ossigeno indipendenti
I Meccanismi microbicici Ossigeno indipendente

Enzimi lisosomiali: lisozima, proteasi, etc.

Polipeptidi antimicrobici:
I Meccanismi microbicicidi Ossigeno indipendenti

Enzimi lisosomiali: lisozima, proteasi, etc.

Polipeptidi antimicrobici:

- Defensine (4 α–defensine)!
I Meccanismi microbicidi Ossigeno indipendenti

Enzimi lisosomiali: lisozima, proteasi, etc.

Polipeptidi antimicrobici:

• Defensine (4 α–defensine)!
I Meccanismi microbicidi Ossigeno indipendenti

Enzimi lisosomiali: lisozima, proteasi, etc.

Polipeptidi antimicrobici:

- Defensine (4 $\alpha$–defensine)!
- Catelicidine!
I Meccanismi microbicici Ossigeno indipendenti

Enzimi lisosomiali: lisozima, proteasi, etc.

Polipeptidi antimicrobici:

- Defensine (4 $\alpha$–defensine)!
- Catelicidine!
I Meccanismi microbicidici Ossigeno indipendenti

Enzimi lisosomiali: lisozima, proteasi, etc.

Polipeptidi antimicrobici:

- Defensine (4 $\alpha$–defensine)!
- Catelicidine!
- BPI (Bactericidal/permeability-increasing proteins)!
Polipeptidi antimicrobici (APP)!!!
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Defensine (4 $\alpha$-defensine): permeabilizzano i microbi!!!
Polipeptidi antimicrobici (APP)!!!

Defensine ($4 \alpha$-defensine): permeabilizzano i microbi!!!
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Catelicidine: permeabilizzano i microbi!!!
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Polipeptidi antimicrobici (APP)!!!

Defensine (4 $\alpha$–defensine): permeabilizzano i microbi!!!

Catelicidine: permeabilizzano i microbi!!!

BPI (Bactericidal/permeabilty-increasing proteins): permeabilizzano i microbi e si legano all’LPS, neutralizzandolo!!!
NEUTROPHILS PLAY A KEY ROLE IN ANTHRAX INFECTIONS!
They can kill Bacillus anthracis by producing a protein called alpha-defensin!

A human neutrophil takes up Bacillus anthracis.
La complessità delle funzioni delle defensine!
### Applicazioni cliniche dei Polipeptidi antimicrobici (APP)!

<table>
<thead>
<tr>
<th>Antimicrobial (polypeptide)</th>
<th>Product name</th>
<th>Indication</th>
<th>Rationale</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>BPI</td>
<td>rBPI\textsubscript{23} (Neuprext, XOMA U.S. LLC, Berkeley, CA)</td>
<td>Meningococcal sepsis</td>
<td>Endotoxemia</td>
<td>III</td>
</tr>
</tbody>
</table>
|                             |                                                  | Prevention of endotoxemia in newborns undergoing cardiopulmonary bypass surgery | 1. CPB-assoc. endotoxemia  
2. Low endogenous BPI in newborns                                      | I/II  |
| Protegrin                   | IBD-367 (IntraBiotics, Palo Alto, CA)            | Prevention of ventilator-associated pneumonia   | Broad-spectrum microbicide for topical use/avoid resistance to systemic agents | III   |
| Indolicidin                 | Omiganan (Micrologix, Vancouver, B.C., Canada)   | Reduction of catheter-associated infections     | Broad-spectrum microbicide for topical use/avoid resistance to systemic agents | III   |
| Lf/Lz                       | (Ventria Bioscience, Sacramento, CA)             | Rotavirus gastroenteritis                       | Lf/Lz activity vs. rotavirus in animal model                               | II    |

CPB, Cardiopulmonary bypass.
I Meccanismi microbicidi Ossigeno dipendenti!
I meccanismi microbicidi Ossigeno dipendenti!

Oxidative burst: Neutrophils kill microbes by producing reactive oxygen species, demonstrated here with the dye nitroblue tetrazolium (NBT).
I Meccanismi microbicidi Ossigeno dipendenti!
Molecular oxygen (O2) is reduced to superoxide (O2−) by electrons pumped into the phagosome by the phagocyte NADPH oxidase.
Molecular oxygen (O2) is reduced to superoxide (O2–) by electrons pumped into the phagosome by the phagocyte NADPH oxidase.
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This charge transfer is compensated by an influx of protons (H+) or other cations.
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The protons are used to reduce superoxide, via SOD (Super Oxide Dismutase), to H2O2, which can be degraded to oxygen and water in a catalase-dependent reaction.
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Alternatively, H2O2 can combine with chloride (Cl–) to form hypochlorous acid (HOCl) in a reaction catalyzed by myeloperoxidase (MPO).
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Alternatively, H2O2 can combine with chloride (Cl–) to form hypochlorous acid (HOCl) in a reaction catalyzed by myeloperoxidase (MPO).
Respiratory Burst (1): Oxygen-dependent Myeloperoxidase-independent reactions!

\[
\begin{align*}
\text{Glucose} + \text{NADP}^+ & \rightarrow \text{Pentose-P} + \text{NADPH} \\
\text{G-6-P-dehydrogenase} & \\
\text{NADPH} + \text{O}_2 & \rightarrow \text{NADP}^{++} + \text{O}_2^- + \text{H}^+ \\
\text{NADPH oxidase} & \\
\text{2O}_2^- + 2\text{H}^+ & \rightarrow \text{H}_2\text{O}_2 + \text{^{1}O}_2 \\
\text{Superoxide dismutase} & \\
\text{2O}_2^- + \text{H}_2\text{O}_2 & \rightarrow \text{OH}^- + \text{OH}^- + \text{^{1}O}_2 \\
\end{align*}
\]

\[
\begin{align*}
\text{superoxide ion} & \\
\text{H}_2\text{O}_2 & \text{hydrogen peroxide} \\
\text{OH}^- & \text{hydroxyl radical} \\
\text{^{1}O}_2 & \text{oxygen singlet} \\
\end{align*}
\]

\text{Reactive Oxygen Species}
Respiratory Burst (2): Oxygen-dependent Myeloperoxidase-dependent reactions!

\[ \text{H}_2\text{O}_2 + \text{Cl}^{-} \rightarrow \text{OCl}^{-} + \text{H}_2\text{O} \]

Myeloperoxidase (MPO)

\[ \text{OCl}^{-} + \text{H}_2\text{O} \rightarrow \text{O}_2 + \text{Cl}^{-} + \text{H}_2\text{O} \]

\[ 2 \text{H}_2\text{O}_2 \xrightarrow{\text{catalase}} \text{H}_2\text{O} + \text{O}_2 \]

(protection mechanism)

OCl\(^{-}\) hypochlorite ion

\(^1\text{O}_2\) oxygen singlet

H\(_2\text{O}_2\) hydrogen peroxide
Nei macrofagi c’è una separazione tra componenti di membrana e citoplasmatici of the NADPH phagocyte oxidase che assicurano che l’attivazione della ossidasi sia sotto controllo in condizioni resting!
Meccanismi-Azoto dipendenti!

Activated macrophages produce also reactive nitrogen species (RNS)!

L’NO è prodotto a partire dall’amminoacido L-arginina in una reazione multi-step catalizzata dall’enzima ossido nitrico sintetasi!

Le tre isoforme dell’ossido nitrico sintetasi!

<table>
<thead>
<tr>
<th></th>
<th>eNOS</th>
<th>nNOS</th>
<th>iNOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Originally cloned from</td>
<td>endothelial cells</td>
<td>neuronal cells</td>
<td>macrophages</td>
</tr>
<tr>
<td>Tissue expression</td>
<td>cardiac myocytes platelets, neutrones</td>
<td>skeletal muscle, neutrophils, VSMC*</td>
<td>cardiac myocytes, glial cells, VSMC*, endothelium, neurones</td>
</tr>
<tr>
<td>Gene encoding and its position</td>
<td>NOS3 7q35-36</td>
<td>NOS1 12q24.2-31</td>
<td>NOS2 17q11.2-12</td>
</tr>
<tr>
<td>Major regulatory mechanism</td>
<td>Ca^{2+} dependent (Ca-calmodulin) Ca^{2+} independent (phosphorylation, palmitoylation)</td>
<td>Ca^{2+} dependent (Ca-dystrophin)</td>
<td>Ca^{2+} independent; transcriptional regulation e.g. by NFκB</td>
</tr>
<tr>
<td>Subcellular localisation</td>
<td>Golgi apparatus plasmalemmal caveolae</td>
<td>cytosol endoplasmic reticulum sarcolema postsynaptic densities caveolae (caveolin 3)</td>
<td>phagosomes</td>
</tr>
</tbody>
</table>
FUNZIONI DELL’OSSIDO NITRICO!

Attività anti-microbica

Proprietà immunoregulatorie (immunosoppressorie)

Danno tissutale

Attività anti-tumorale

Arginina → citrullina + NO

Arginina → iNOS
Activated macrophages produce reactive oxygen (ROS) and reactive nitrogen species (RNS)

DNA damage, lipid peroxidation, mitochondrial damage

anti-microbial, and anti-tumor activity, tissue damage
Phagocyte deficiencies are associated with augmented susceptibility to extracellular bacteria and fungi

<table>
<thead>
<tr>
<th>Type of defect/name of syndrome</th>
<th>Associated infectious or other diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocyte adhesion deficiency</td>
<td>Widespread pyogenic bacterial infections</td>
</tr>
<tr>
<td>Chronic granulomatous disease</td>
<td>Intracellular and extracellular infection, granulomas</td>
</tr>
<tr>
<td>G6PD deficiency</td>
<td>Defective respiratory burst, chronic infection</td>
</tr>
<tr>
<td>Myeloperoxidase deficiency</td>
<td>Defective intracellular killing, chronic infection</td>
</tr>
<tr>
<td>Chediak–Higashi syndrome</td>
<td>Intracellular and extracellular infection, granulomas</td>
</tr>
</tbody>
</table>

Figure 11-14 Immunobiology, 6/e. (© Garland Science 2005)
Leukocyte Adhesion Deficiencies (LAD 1-2-3)!!!!
A) Stable adhesion by leukocyte integrins, absent in **LAD-1**, to ligands on the endothelium results in leukocyte arrest.
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Leukocyte Adhesion Deficiencies (LAD 1-2-3)!!!

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B) When the leukocytes slow down because of transient interactions between selectins and their glycosylated ligands, means that they are defective in LAD-2.
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A) Stable adhesion by leukocyte integrins, absent in \textbf{LAD-1}, to ligands on the endothelium results in leukocyte arrest.

B) When the leukocytes slow down because of transient interactions between selectins and their glycosylated ligands, means that they are defective in \textbf{LAD-2}.

C) Activation of blood cell integrins is decreased in \textbf{LAD-3}.
**Leukocyte Adhesion Deficiency-I (LAD-I)!!!**

Table 20-2

<table>
<thead>
<tr>
<th>Property</th>
<th>INTEGRIN MOLECULES*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LFA-1</td>
</tr>
<tr>
<td>CD designation</td>
<td>CD11a/CD18</td>
</tr>
<tr>
<td>Subunit composition</td>
<td>αLβ2</td>
</tr>
<tr>
<td>Subunit molecular mass (kDa)</td>
<td></td>
</tr>
<tr>
<td>α chain</td>
<td>175,000</td>
</tr>
<tr>
<td>β chain</td>
<td>95,000</td>
</tr>
<tr>
<td>Cellular expression</td>
<td>Lymphocytes, Monocytes, Macrophages, Granulocytes, Natural killer cells</td>
</tr>
<tr>
<td>Ligand</td>
<td>ICAM-1 (CD 54), ICAM-2 (CD 102)</td>
</tr>
<tr>
<td>Functions inhibited with monoclonal antibody</td>
<td>Extravasation, CTL killing, T-B conjugate formation, ADCC</td>
</tr>
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*CR3 = type 3 complement receptor, also known as Mac-1; CR4 = type 4 complement receptor, also known as gp150/95; LFA-1, CR3, and CR4 are heterodimers containing a common β chain but different α chains designated L, M, and X, respectively.*
# Leukocyte Adhesion Deficiency-I (LAD-I)!!!!

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<tr>
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<tr>
<td><strong>CD designation</strong></td>
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<td>CD11b/CD18</td>
<td>CD11c/CD18</td>
</tr>
<tr>
<td><strong>Subunit composition</strong></td>
<td>αLβ2</td>
<td>αMβ2</td>
<td>αXβ2</td>
</tr>
<tr>
<td><strong>Subunit molecular mass (kDa)</strong></td>
<td>175,000, 95,000</td>
<td>165,000, 95,000</td>
<td>150,000, 95,000</td>
</tr>
<tr>
<td><strong>Cellular expression</strong></td>
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</tr>
<tr>
<td><strong>Ligand</strong></td>
<td>ICAM-1 (CD 54), ICAM-2 (CD 102)</td>
<td>C3bi</td>
<td>C3bi</td>
</tr>
<tr>
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<td>Monocytes</td>
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<td></td>
<td>Monocytes</td>
<td>Macrophages</td>
<td>Macrophages</td>
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<td></td>
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<tr>
<td></td>
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Leukocyte Adhesion Deficiency-I (LAD-I)!!!!

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<td>Monocytes</td>
<td>Monocytes</td>
</tr>
<tr>
<td></td>
<td>Monocytes</td>
<td>Macrophages</td>
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<td>Macrophages</td>
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**Leukocyte Adhesion Deficiency-I (LAD-I)**

*Gene defect in $\beta_2$ integrin gene*

### TABLE 20-2: Properties of integrin molecules that are absent in leukocyte-adhesion deficiency

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<td>CD11b/CD18</td>
<td>CD11c/CD18</td>
</tr>
<tr>
<td>Subunit composition</td>
<td>$\alpha L\beta 2$</td>
<td>$\alpha M\beta 2$</td>
<td>$\alpha X\beta 2$</td>
</tr>
<tr>
<td>Subunit molecular mass (kDa)</td>
<td>175,000</td>
<td>165,000</td>
<td>150,000</td>
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<tr>
<td>$\alpha$ chain</td>
<td>95,000</td>
<td>95,000</td>
<td>95,000</td>
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<td></td>
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Leukocyte Adhesion Deficiency-I (LAD-I)!!!

- Gene defect in $\beta_2$ integrin gene!
- Patients suffer from recurrent, life-threatening bacterial infections!
**Leukocyte Adhesion Deficiency-I (LAD-I)!!!**

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- Gene defect in β2 integrin gene!
- Patients suffer from recurrent, life-threatening bacterial infections!
- They show impaired accumulation of myeloid leukocytes at extravascular sites!
Tissue necrosis after removal of the umbilical stump. Patients with LAD-I commonly present with delayed separation of the umbilical cord, often followed by omphalitis, resulting in tissue necrosis in some cases.
Tissue necrosis after removal of the umbilical stump. Patients with LAD-I commonly present with delayed separation of the umbilical cord, often followed by omphalitis, resulting in tissue necrosis in some cases.

**Tabella 27.5**
Leucocyte Adhesion Deficiency (LAD)-1/Criteri Diagnostici ESID/PSID

<table>
<thead>
<tr>
<th>Diagnosi definitiva:</th>
<th>Pazienti di sesso maschile o femminile con diminuzione dell’intensità di espressione di CD18 nei neutrofili (&lt;5% rispetto al controllo) e almeno uno dei seguenti parametri:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• mutazioni nel gene per l’integrina β2;</td>
</tr>
<tr>
<td></td>
<td>• assenza di mRNA per integrina β2 nei leucociti.</td>
</tr>
<tr>
<td>Diagnosi probabile:</td>
<td>pazienti di sesso maschile o femminile con diminuzione dell’intensità di espressione di CD18 nei neutrofili (&lt;5% rispetto al controllo) e almeno uno dei seguenti parametri:</td>
</tr>
<tr>
<td></td>
<td>• ritardata guarigione delle ferite e/o separazione del cordone ombelicale;</td>
</tr>
<tr>
<td></td>
<td>• leucocitosi (GB &gt;25.000/ml);</td>
</tr>
<tr>
<td></td>
<td>• infezioni batteriche e/o fungine ricorrenti.</td>
</tr>
<tr>
<td>Diagnosi possibile:</td>
<td>bambini con leucocitosi (GB &gt;25.000/mcL) e almeno uno dei seguenti:</td>
</tr>
<tr>
<td></td>
<td>• infezioni profonde;</td>
</tr>
<tr>
<td></td>
<td>• diminuita o assente formazione di pus nei siti infetti;</td>
</tr>
<tr>
<td></td>
<td>• infezioni batteriche e/o fungine ricorrenti.</td>
</tr>
</tbody>
</table>

La diagnosi è considerata definitiva o probabile quando nel singolo paziente le probabilità di confermare la diagnosi nei successivi 20 anni sono rispettivamente 98% e 85%. I pazienti con una diagnosi possibile sono quelli che hanno solo alcuni aspetti clinici e/o laboratoristici della sindrome.
Leukocyte Adhesion Deficiency-2 (LAD-2) FEATURES!

Clinical stigmata in patients with LAD-2. Defective fucosylation results in growth retardation and a coarse face. Long eyelashes, a broad and depressed nasal bridge, a simian crease, and dorsally positioned second toes are the clinical stigmata of a patient with LAD-2.

Leukocyte Adhesion Deficiency-3 (LAD-3) FEATURES!

Leukocyte adhesion deficiencies.
van de Vijver E, van den Berg TK, Kuijpers TW.

Not all patients with LAD-3 show osteopetrosis. Vertebrae and hip joint of an osteopetrotic patient (A, B) compared with the lumbar vertebrae and pelvis of a patient who is kindlin-3-deficient without osteopetrosis (C).
Leukocyte Adhesion Deficiency-3 (LAD-3) FEATURES!

Not all patients with LAD-3 show osteopetrosis. Vertebrae and hip joint of an osteopetrotic patient (A, B) compared with the lumbar vertebrae and pelvis of a patient who is kindlin-3–deficient without osteopetrosis (C).

Abnormal erythrocyte phenotype. Dacrocytes (teardrop–shaped; left 2 arrowheads) and elliptocytes (right arrowhead) characterize the erythrocyte population of LAD-3, although the phenotype is less severe than in kindlin-3–/– mice.
Chronic Granulomatous Disease (CGD)!
Chronic Granulomatous Disease (CGD)!

- Genetic defect in NADPH oxidase subunit genes!
Chronic Granulomatous Disease (CGD)!

- Genetic defect in NADPH oxidase subunit genes!
Chronic Granulomatous Disease (CGD)!

- Genetic defect in NADPH oxidase subunit genes!
- Characterized by greatly increased susceptibility to severe bacterial and fungal infections (Aspergillus)!
The Chédiak–Higashi syndrome (CHS)
The Chédiak–Higashi syndrome (CHS)
La Chédiak–Higashi syndrome (CHS) è il 3 Tipo di SINDROME EMOFAGOCITICA (HS) GENETICA/EREDITARIA!
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(Inherited HS is fatal, if left untreated)!!!!!
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CHS is a rare autosomal recessive condition that is characterized by hypopigmentation and onset of HS.
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(Inherited HS is fatal, if left untreated)!!!!!

CHS is a rare autosomal recessive condition that is characterized by hypopigmentation and onset of HS.

The protein defective in CHS patients and in the beige mouse model has been identified as the 419-kDa CHS1/Lyst protein which control lysosome/membrane fusion.
The Chédiak–Higashi syndrome (CHS) is a defective vesicle transport and an immunological disorder!

The striking phenotype of cells is the presence of giant intracytoplasmic granulations in all granulated cells, including hematopoietic cells and melanocytes.

Diagram comparing secretion from cytotoxic T lymphocytes (CTLs) and from melanocytes.

Chédiak-Higashi syndrome: a defect in granulogenesis!

Healthy!

Chédiak-Higashi patient!

Neutrophils!

Hair!
New functions of phagocytes!
New functions of phagocytes!

Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality!!!
The NETosis!
The NETosis!
Cell Death Differ.  

Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality.

Remijsen Q, Kuijpers TW, Wirawan E, Lippens S, Vandenabeele P, Vanden Berghe T. Department of Biomedical Molecular Biology, Molecular Signaling and Cell Death Unit, Ghent University, Ghent, Belgium.
Dying for a cause: NETosis, mechanisms behind an antimicrobial cell death modality.

Remijsen Q, Kuijpers TW, Wirawan E, Lippens S, Vandenabeele P, Vanden Berghe T. Department of Biomedical Molecular Biology, Molecular Signaling and Cell Death Unit, Ghent University, Ghent, Belgium.

Guimarães-Costa AB, Nascimento MT, Wardini AB, Pinto-da-Silva LH, Saraiva EM. Instituto de Microbiologia Paulo de Góes, Universidade Federal do Rio de Janeiro (UFRJ), 21941-901 Rio de Janeiro, RJ, Brazil.

Nectosis is a recently described type of neutrophil death occurring with the release to the extracellular milieu of a lattice composed of DNA associated with histones and granular and cytoplasmic proteins. These webs, initially named neutrophil extracellular traps (NETs), ensnare and kill microorganisms. Similarly, other cell types, such as eosinophils, mast cells, and macrophages, can also dye by this mechanism; thus, it was renamed as ETosis, meaning death with release of extracellular traps (ETs). Here, we review the mechanism of NETosis/etosis, emphasizing its role in diseases caused by protozoan parasites, fungi, and viruses.
The NETosis is a new function of neutrophils and their products!
The NETosis is a new function of neutrophils and their products!

Neutrophils generate extracellular fibers called NETs that kill bacterial pathogens without the need for phagocytosis!
The NET (NEUTROPHIL EXTRACELLULAR TRAP) contacts bacterial pathogens!

Brinkmann V, Reichard U, Fauler B, Goosmann C, Uhlemann Y, Weiss D, Weinrauch Y, Zychlinsky A

Neutrophil extracellular traps kill bacteria

Science, 5 March 2004
The NET (NEUTROPHIL EXTRACELLULAR TRAP) involves bacterial pathogens!

Brinkmann V, Reichard U, Fauler B, Goosmann C, Uhlemann Y, Weiss D, Weinrauch Y, Zychlinsky A

**Neutrophil extracellular traps kill bacteria**

*Science, 5 March 2004*
NETs can trap Gram- and Gram+ bacteria, and fungi!!
NETs can trap Gram- and Gram+ bacteria, and fungi!!
NETs can trap Gram- and Gram+ bacteria, and fungi!!

Shigella flexneri!
NETs can trap Gram- and Gram+ bacteria, and fungi!!

- Shigella flexneri!
- S. aureus!
- C. albicans!
**Extracellular traps: Chromatin in host defense**

*MEK–ERK kinase pathway (Hakkim et al., 2011)* and *Rac2 cells produce NETs, showing that the pathway can be rescued (Oehmcke et al., 2009), or lipophosphoglycans from to require attachment of neutrophils to a substrate that stimu-

Infections (Fuchs et al., 2007; Bianchi et al., 2009). Interestingly, produce ROS or make NETs. These chronic granulomatous dis-

tions in any of the subunits of the PHOX complex cannot

*Neutrophils of patients with immune de*

*NET formation requires the production of ROS. The

*Molecularly, the few events that have been shown to be*

*Extracellular traps: Chromatin in host defense*
Pus consists of numerous neutrophils in various stages of NETosis surrounded by NETs. Semithin cryosection of pus from a Molluscum contagiosum lesion stained for NE (green) and chromatin (red). Bar, 20 µm.
Quali sono i meccanismi molecolari della NETosis?
Neutrophils were stimulated with PMA, and a z stack was generated for 2 h and 25 min on a confocal microscope. Directly labeled antibody fragments against NE (green) and chromatin (red) in the supernatant depict formation of NETs in the final phase.

Neutrophils were stimulated with PMA, and a z stack was generated for 2 h and 25 min on a confocal microscope. Directly labeled antibody fragments against NE (green) and chromatin (red) in the supernatant depict formation of NETs in the final phase.

The steps leading to Neutrophil Extracellular Traps (NET) formation!
The steps leading to Neutrophil Extracellular Traps (NET) formation!
The steps leading to Neutrophil Extracellular Traps (NET) formation:

1. Nuclear membrane dissolution
2. Nuclear material fills most of the cell and mixes with the contents of the granules
The steps leading to Neutrophil Extracellular Traps (NET) formation!

1. Nuclear membrane dissolution
2. Nuclear material fills most of the cell and mixes with the contents of the granules
3. Cell rounds up, contracts, and releases NETs
The biochemical pathways leading to Neutrophil Extracellular Traps (NET) formation!

After stimulation of receptors (A), neutrophils adhere to the substrate (B) and mobilize granule components, namely NE and MPO (C). Granules are depicted as red circles. Histones in the nucleus get processed, and the intracellular membranes disintegrate. Finally, the cell membrane ruptures, and the mixture of cytoplasm and nucleoplasm gets expelled to form NETs (D).
NETosis, the process wherein neutrophils release highly decondensed chromatin called neutrophil extracellular traps (NETs), has gained much attention as an alternative means of killing bacteria. In vivo, NETs are induced by bacteria and pro-inflammatory cytokines. We have reported that peptidylarginine deiminase 4 (PAD4), an enzyme that converts Arg or monomethyl-Arg to citrulline in histones, is essential for NET formation. The areas of extensive chromatin decondensation along the NETs were rich in histone citrullination. Here, upon investigating the effect of global citrullination in cultured cells, we discovered that PAD4 overexpression in osteosarcoma U2OS cells induces extensive chromatin decondensation independent of apoptosis. The highly decondensed chromatin is released to the extracellular space and stained strongly by a histone citrulline-specific antibody. The structure of the decondensed chromatin is reminiscent of NETs but is unique in that it occurs without stimulation of cells with pro-inflammatory cytokines and bacteria. Furthermore, histone citrullination during chromatin decondensation can dissociate heterochromatin protein 1 beta (HP1β) thereby offering a new molecular mechanism for understanding how citrullination regulates chromatin function. Taken together, our study suggests that PAD4 mediated citrullination induces chromatin decondensation, implicating its essential role in NET formation under physiological conditions in neutrophils.
Quali sono i componenti molecolari della NET?
The ultrastructure of NETs is unusual; NETs consist of smooth filaments with a diameter of $\sim 17$ nm, composed of stacked, and probably modified, nucleosomes. This backbone is studded with globular domains with a diameter of $\sim 50$ nm made of granular proteins. This morphology in high-resolution scanning electron microscopy easily differentiates NETs from other fibrous structures such as fibrin. Interestingly, unfixed, fully hydrated NETs have a cloud-like appearance and occupy a space that is 10–15-fold bigger than the volume of the cells they originate from, reflecting what they may look like in vivo when space is available, for example in the lung alveolus.

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LA NET (NEUTROPHIL EXTRACELLULAR TRAP) È FORMATA DA PROTEINE DEI GRANULI e DA CROMATINA!
The humoral pattern recognition receptor PTX3 is stored in neutrophil granules and localizes in extracellular traps!

Sébastien Jaillon, Giuseppe Peri, Yves Delneste, Isabelle Frémaux, Andrea Doni, Federica Moalli, Cecilia Garlanda, Luigina Romani Hugues Gascan, Silvia Belloccio, Silvia Bozza, Marco A. Cassatella, Pascale Jeannin and Alberto Mantovani
LA NET (NEUTROPHIL EXTRACELLULAR TRAP) È FORMATA DA CROMATINA!

Visualizing NETs using chromatin antibodies or DNA-intercalating dyes.
Neutrophil extracellular traps: Is immunity the second function of chromatin?

Volker Brinkmann and Arturo Zychlinsky

Microscopy Core Facility
Department of Cellular Microbiology, Max Planck Institute for Infection Biology, 10117 Berlin, Germany
Neutrophil Extracellular Traps: an additional antibacterial weapon!

- Phagolysosome contents include: NADPH oxidase, elastase, gelatinase, BPI, azurocidin, lactoferrin, cathepsin G, defensins, myeloperoxidase and hydrochloric acid.
- Azurophilic (primary) granules: myeloperoxidase, cathepsins, azurocidin, BPI elastase, proteinase 3 and defensins.
- Specific (secondary) granules: collagenase, heparinase, gelatinase, lysozyme and sialidase.
- Gelatinase (tertiary) granules: gelatinase and lysozyme.
Anche gli eosinofili e i basofili formano la NET!

Monosodium urate crystals induce extracellular DNA traps in neutrophils, eosinophils, and basophils but not in mononuclear cells.

Schorn C, Janko C, Latzko M, Chaurio R, Schett G, Herrmann M.

Neutrophil extracellular traps: double-edged swords of innate immunity.

Kaplan MJ, Radic M.
Division of Rheumatology, Department of Internal Medicine, University of Michigan Medical School, Ann Arbor, MI 48109, USA
Spectacular images of neutrophils ejecting nuclear chromatin and bactericidal proteins, in response to microbes, were first reported in 2004. As externalized chromatin could entangle bacteria, these structures were named neutrophil extracellular traps (NETs). Subsequent studies identified microorganisms and sterile conditions that stimulate NETs, as well as additional cell types that release extracellular chromatin. The release of NETs is the most dramatic stage in a cell death process called NETosis.
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Neutrophil extracellular traps and their role in the development of chronic inflammation and autoimmunity!
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This review summarizes current knowledge concerning the general characteristics of NETs, their antimicrobial properties, and their role in the development of chronic inflammatory processes that underlie the pathogenesis of psoriasis and atherosclerosis.
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The Phagocytes!

mononuclear

Polymorphonuclear (PMN)

Monocyte (peripheral blood)
- Lysosome
- Nucleus
- Phagosome

Neutrophil
- Glycogen
- Secondary granule
- Primary azurophilic granule
- Multilobed nucleus
- Phagosome

50-70% of peripheral blood leukocytes, half-life: 2-3 d, even less!

Macrophage (tissues)
- Pseudopodia
- Phagolysosome
- Lysosome
- Phagosome
LE CITOCHINE E CHEMOCHINE INFiammatorie!
Kinetic of Pro-inflammatory cytokine and chemokine production by activated phagocytes!
<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Main producer</th>
<th>Acts upon</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lymphocytes</td>
<td>Enhances responses</td>
</tr>
<tr>
<td>IL-1</td>
<td>Macrophages</td>
<td>Liver</td>
<td>Induces acute-phase protein secretion</td>
</tr>
<tr>
<td></td>
<td>Keratinocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>Macrophages</td>
<td>Lymphocytes</td>
<td>Enhances responses</td>
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<tr>
<td></td>
<td>Dendritic cells</td>
<td>Liver</td>
<td>Induces acute-phase protein secretion</td>
</tr>
<tr>
<td>CXCL8</td>
<td>Macrophages</td>
<td>Phagocytes</td>
<td>Chemoattractant for neutrophils</td>
</tr>
<tr>
<td>(IL-8)</td>
<td>Dendritic cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-12</td>
<td>Macrophages</td>
<td>Naive T cells</td>
<td>Diverts immune response to type 1, proinflammatory, cytokine secretion</td>
</tr>
<tr>
<td></td>
<td>Dendritic cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TNF-α</td>
<td>Macrophages</td>
<td>Vascular endothelium</td>
<td>Induces changes in vascular endothelium (expression of cell-adhesion molecules (E- and P-selectin), changes in cell–cell junctions with increased fluid loss,</td>
</tr>
<tr>
<td></td>
<td>Dendritic cells</td>
<td></td>
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</tbody>
</table>
LE CITOCHINE E CHEMOCHINE INFiammatorie MEDIANO GLI EFFETTI LOCALI E SISTEMICI DELL’INFiamMAZIONE!

**Figure 2-46 Immunobiology, 6/e. (© Garland Science 2005)**
Local effects of TNF$_\alpha$ and IL-1$\beta$!!!

- Cytokines produced by macrophages cause dilation of local small blood vessels
- Leukocytes move to periphery of blood vessel as a result of increased expression of adhesion molecules
- Leukocytes extravasate at site of infection
- Blood clotting occurs in the microvessels

-† vasodilation
-† enhanced expression of vascular addressins
Circulating effects of TNFα and IL-1β: PATOGENESI DELLA FEBBRE!
Fibrinogen and erythrocyte sedimentation rate (ESR) or VES!

**Fibrinogen levels become elevated in acute phase up to values of occasional over 1.0 g/dL.** In this case also becomes markedly elevated erythrocyte sedimentation rate (ESR): it is believed that 60-70% of the increase is due to the ESR of fibrinogen due to the neutralizing effect of the latter on the sialic acid residues of red blood cells that are known to inhibit the erythrocyte aggregation.
Systemic effects of IL-1β, TNFα, and IL-6

The acute phase response!
FEBBRE, VES e LEUCOCITOSI SONO I MARCATORI INFIAMMATORI SISTEMICI!
Pathological consequences of Systemic Inflammatory response (SIRS) are:

• Septic shock;

• ARDS;

• Multiple organ dysfunction (MOD) and Multiple organ failure (MOF)
SHOCK SETTICO: endototossico ed esotossico!

Pathological consequences of inflammatory response to systemic LPS: the septic shock

- endototossico

Septic shock is classically triggered by Gram- bacteria (TLR-4/LPS); Gram+ bacteria too can induce a systemic inflammatory response (SuperAg, TLR2/ lipoproteins)!

- esotossico
Toxic Systemic effects of TNFα and IL1β: SHOCK SETTICO!

- vasodilation
- low cardiac output
- formation of thrombi
- intravascular coagulation
SEVERE SEPSYS CAN ACTIVATE ALSO ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)!
SEVERE SEPSIS HEAVILY AFFECT VASCULAR FUNCTION: THE PATHOGENETIC NETWORKS!
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Pathogenetic networks in shock!
SEVERE SEPSIS HEAVILY AFFECT VASCULAR FUNCTION: THE PATHOGENETIC NETWORKS!

Pathogenetic networks in shock!
Lipopolysaccharide (LPS) and other microbial components simultaneously activate multiple parallel cascades that contribute to the pathophysiology of adult respiratory distress syndrome (ARDS) and shock.
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SEVERE SEPSIS HEAVILY AFFECT VASCULAR FUNCTION: THE PATHOGENETIC NETWORKS!

Pathogenetic networks in shock!

Lipopolysaccharide (LPS) and other microbial components simultaneously activate multiple parallel cascades that contribute to the pathophysiology of adult respiratory distress syndrome (ARDS) and shock.

The combination of poor myocardial contractility, impaired peripheral vascular tone and microvascular occlusion leads to tissue hypoperfusion and inadequate oxygenation, and thus to Multiple organ dysfunction (MOD) and Multiple organ failure (MOF).
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Simplified clinical course of sepsis. Progression of disease is complex, nonlinear, and varies from one patient to another. Shown is an outline of selected landmark events and processes that appear to be common among patients and some animal models. DIC, disseminated intravascular coagulation.