We have analyzed how inflammation is activated and links innate and adaptive immunity.......

Foreign structures  Damaged self

Recognition

Innate immunity  Adaptive immunity

Inflammation

Vascular effects
Inflammatory cell accumulation
Destruction of the initiating stimulus
Removal (including the inflammatory cells)
Repair (restoration of normal structure and function)
...NOW WE HAVE TO ANALYZE THE STOP AND THE RESOLUTION OF THE INFLAMMATION AND THE CONTROL OF INNATE IMMUNITY AND OF THE INFLAMMATION!
THE ACTIVATION AND

PROSTAGLANDINS, LEUCOTRIENS, TROMBOXANS, IL1, IL6, TNF, SP, CATECOLAMINS, NGF!
THE RESOLUTION OF INFLAMMATION AND THE CONTROL OF THE INNATE IMMUNITY AND THE INFLAMMATION!

LIPOXINS, RESOLVINS, PROTECTINS, MARESINS

IL1RA
IL10
TGF beta
THE RESOLUTION OF INFLAMMATION AND THE CONTROL OF THE INNATE IMMUNITY AND THE INFLAMMATION!

LIPOXINS, RESOLVINS, PROTECTINS, MARESINS

IL1RA
IL10
TGF beta
RISOLUZIONE DELLA RISPOSTA INFIAMMATORIA ED IMMUNITARIA NATURALE E LORO MECCANISMI DI CONTROLLO.

Prof. Fabrizio Mainiero

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

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Il materiale presente in questo documento viene distribuito solamente per uso interno ed esclusivamente a scopo didattico.
Guanigione
Risoluzione
Infiammazione acuta
Mediatori
Infiammazione cronica
Infezioni persistenti
Malattie autoimmuni
Risoluzione
Guarigione
Lesione
Mediatori
RISOLUZIONE DELL’INFIAMMAZIONE ACUTA!

1. Ripristino della normale permeabilità vascolare
2. Drenaggio dei liquidi e delle proteine del l’essudato da parte dei vasi linfatici
3. Pinocitosi
4. Fagocitosi
5. Eliminazione dei macrofagi
RISOLUZIONE DELL’INFIAMMAZIONE ACUTA!

FATTI PRINCIPALI
Risoluzione

- Risultato finale è il ripristino della normale struttura e funzione, senza esito cicatriziale.
- L’essudato infiammatorio acuto è rimosso per fluidificazione e fagocitosi.
- Lo stroma di sostegno deve essere intatto.
- Le cellule danneggiate devono essere capaci di rigerare.
The apoptosis of infiltrating polymorphonuclear cells (PMNs, neutrophils), their efferocytosis by tissue and monocyte-derived macrophages (MDMs) and either the incorporation of these myeloid cells into the local population or their recirculation via lymph or blood!
This review provides a summary on the basics of inflammation, the structure of lymphatics and their molecular markers, human inflammation-associated diseases and their relation to lymphatics, animal models to study the interaction of lymphatics and inflammation, and finally inflammation-associated molecules expressed in LECs. The integration of lymphatics into inflammation research opens up an exciting new field with great clinical potential.
Resolution of inflammation in 1980

«resolution is a passive event, the default evolution of an acute inflammatory reaction with exudate resolved and no damage to stroma»
Oggi è noto che l’inflamazione, la sua risoluzione e la risposta immunitaria innata sono controllate da:

- Mediatori lipidici!
- Citochine!
- Pentraxine!
- Sistema neuroendocrino!
Resolution of inflammation: state of the art, definitions and terms.

Serhan CN, Brain SD, Buckley CD, Gilroy DW, Haslett C, O'Neill LA, Perretti M, Rossi AG, Wallace JL.
Acute inflammation activation and resolution and associated **LIPID** mediators!

LIPOXINS, RESOLVINS, PROTECTINS, MARESINS
Acute inflammation activation and resolution and associated **LIPID** mediators!

* LIPOXINS, RESOLVINS, PROTECTINS, MARESINS
All the LIPID mediators derive from Omega-6 or Omega-3 fatty acids (PFUA)!
I MEDIATORI LIPIDICI CHE BLOCCANO L’INFIAMMAZIONE ..........

- LIPOSSINE
- 15-EPI-LIPOSSINE (ATL)
- RESOLVINE
- PROTECTINE
- MARESINE
Resolution of inflammation is an active process
RECENTEMENTE SI È OSSERVATO CHE DALL’AA OLTRE AI LEUCOTRIENI (LT) SI FORMANO ANCHE LE LIPOSSINE (LX) (PER L’AZIONE COMBINATA DELLE 5- 12- e 15-LIPOOSSIGENASI)
RECENTEMENETE SI È OSSERVATO CHE DALL’AA OLTRE AI LEUCOTRIENI (LT) SI FORMANO ANCHE LE LIPOSSINE (LX) (PER L’AZIONE COMBINATA DELLE 5- 12- e 15-LIPOOSSIGENASI)

OMEGA-6 ACIDI GRASSI POLINSATURI (PFUA) E RISPOSTA ANTI-INFIAMMATORIA!

![Diagram of arachidonic acid metabolism](image)
FORMAZIONE DELLE LIPOSSINE (LX)
(PER L’AZIONE COMBINATA DELLE 15- e 5-
LIPOOSSIGENASI):
COOPERAZIONE TRA PMN E Eosinofili, MONOCITI/
FORMAZIONE DELLE LIPOSSINE (LX)
(PER L’AZIONE COMBINATA DELLE 15- e 5-
LIPOOSSIGENASI):
COOPERAZIONE TRA PMN E Eosinofili, MONOCITI/

Lipoxin A₄
FORMAZIONE DELLE LIPOSSINE (LX) (PER L’AZIONE COMBINATA DELLE 15- e 5-LIPOOSSIGENASI): COOPERAZIONE TRA PMN E Eosinofili, MONOCITI/
FORMAZIONE DELLE LIPOSSINE (LX)
PER L’AZIONE COMBINATA
DELLE 5- e 12-LIPOOSSIGENASI:
COOPERAZIONE TRA PMN E PIASTRINE!!!!

Cell-Cell Interactions

Neutrophil

LTA₄
Hydrolase

LTB₄

Thrombin

LXA₃

LXB₄

12-LO

Suicide inactivation

Platelet

Chemotactic peptides

cPLA₂

C20:4

Ca²⁺
FORMAZIONE DELLE LIPOSSINE (LX) PER L’AZIONE COMBINATA DELLE 5- e 12-LIPOOSSIGENASI: COOPERAZIONE TRA PMN E PIASTRINE!!!!
Oltre alle LIPOSSINE si possono formare anche le Aspirin-triggered 15-epi-lipoxins (ATL) per l’azione combinata delle COX2 e delle 5-LIPOOSSIGENASI!!!
Oltre alle LIPOSSINE si possono formare anche le Aspirin-triggered 15-epi-lipoxins (ATL) per l’azione combinata delle COX2 e delle 5-LIPOOSSIGENASI!!!
OMEGA-6 ACIDI GRASSI POLINSATURI (PFUA) E RISPOSTA ANTI-INFIAMMATORIA!

Le Aspirin-triggered 15-epi-lipoxins (ATL) A4 e B4 !!!

OMEGA-6 ACIDI GRASSI POLINSATURI (PFUA) E RISPOSTA ANTI-INFIAMMATORIA!

Le Aspirin-triggered 15-epi-lipoxins (ATL) A4 e B4 !!!
Le Aspirin-triggered 15-epi-lipoxins (ATL) A4 e B4 !!!

OMEGA-6 ACIDI GRASSI POLINSATURI (PFUA) E RISPOSTA ANTI-INFIAMMATORIA!

Transcellular biosynthesis of aspirin-triggered 15-epi-lipoxins

When aspirin acetylates COX-2 PG production is blocked, but the acetylated COX-2 (in epithelial and endothelial cells) converts arachidonate to 15-HETE, which is then converted by 5-LO (in leukocytes) in 15-epi-lipoxins

Serhan CN.
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LE LIPOSSINE E LE 15-EPI-LIPOSSINE (ATL) BLOCCANO L’INFIAMMAZIONE!!!!!!
Lipid mediators in the progression and outcomes of the inflammatory response:

LE LIPOSSINE E LE 15-EPI-LIPOSSINE (ATL)
BLOCCANO L’INFIAMMAZIONE!!!!!!
**Biological (proresolving) properties of lipoxins and aspirin-triggered 15-epi-lipoxins**

LXs and ATL were shown to exert their anti-inflammatory and pro-resolution effects by:

(i) stopping infiltration and activation of PMNs (Levy et al., 2001; Perretti et al., 2002)
(ii) stimulating macrophage phagocytosis of apoptotic PMNs (Godson et al., 2000)
(iii) reducing the synthesis of the pro-inflammatory cytokines (TNFα: Hachicha et al., 1999; IL-8: Gronert et al., 1998)
(iv) upregulating the synthesis of anti-inflammatory cytokines TGFβ (Mitchell et al., 2002)

LXs and ATL were shown to exert their anti-inflammatory and pro-resolution effects in various experimental models of inflammations, as well as in human diseases, including:

- glomerulonephritis (O'Meara & Brady, 1997)
- colitis (Gewirtz et al., 2002)
- ischemia/reperfusion injury (Leonard et al., 2002)
- cutaneous inflammation models (Schottelius et al., 2002)
- periodontitis (Pouliot et al., 2000)
- acute pleuritis (Paul-Clark et al., 2004)
- peritonitis (Bannenberg et al., 2004)
- cystic fibrosis (Karp et al., 2005)
- asthma (Levy, 2005)
- wound healing processes in the eye (Gronert, 2005)
- skin edema formation in mice (Guilford & Parkinson, 2005)
- inflammation-induced hyperalgesia in rats (Svensson et al., 2007)

Lipid mediators class switching

OMEGA-6 ACIDI GRASSI POLINSATURI (PFUA) E RISPOSTA PRO-ED ANTI-INFIAMMATORIA!
Key eicosanoids that play pivotal roles in initiating inflammation and in its resolution!

**OMEGA-6 ACIDI GRASSI POLINSATURI (PFUA) E RISPOSTA PRO- ED ANTI-INFIAMMATORIA!**

<table>
<thead>
<tr>
<th>Signs</th>
<th>“Go” Signals</th>
<th>“Stop” Signals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotaxis, leukocyte</td>
<td>LTB₄, HETEs</td>
<td>LXA₄, LXB₄</td>
</tr>
<tr>
<td>Vascular permeability</td>
<td>LTC₄, LTD₄</td>
<td>LXA₄</td>
</tr>
<tr>
<td>Pain and hyperalgesia</td>
<td>PGE₂, PGI₂, LTB₄</td>
<td>LXA₄</td>
</tr>
<tr>
<td>Local heat and systemic fever</td>
<td>PGE₂, PGI₂</td>
<td>LXA₄</td>
</tr>
<tr>
<td>Vasodilation (erythema)</td>
<td>PGI₂, PGE₁, PGE₂, PGD₂</td>
<td>LXA₄, LXB₄, LTB₄</td>
</tr>
<tr>
<td>Edema (swelling)</td>
<td>PGE₂, LTB₄</td>
<td></td>
</tr>
</tbody>
</table>
Resolvins and protectins: mediating solutions to inflammation.


Resolvins and protectins are recently identified molecules that are generated from omega-3 PUFA precursors and can orchestrate the timely resolution of inflammation in model systems.
Overview of the pathways of lipid mediator synthesis from EPA and DHA

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HPEPE, hydroperoxyeicosapentaenoic acid; LT, leukotriene; PG, prostaglandin.

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OMEGA-3 ACIDI GRASSI POLINSATURI (PFUA) E RISPOSTA ANTI-INFIAMMATORIA: LE RESOLVINE, PRODOTTE PER L’AZIONE DELLE COX2 E DELLE 5-LIPOOSSIGENAS!

Overview of the pathways of lipid mediator synthesis from EPA and DHA

DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HEPE, hydroxyeicosapentaenoic acid; HPEPE, hydroperoxyeicosapentaenoic acid; LT, leukotriene; PG, prostaglandin.

OMEGA-3 ACIDI GRASSI POLINSATURI (PFUA) E RISPOSTA ANTI-INFIAMMATORIA: LE PROTECTINE!

LE PROTECTINE SONO PRODOTTE DALLE LIPOOSSIGENASI A PARTIRE DAL DHA (acido docosahexaenoico)!!!

Resolvins and protectins in the termination program of acute inflammation.
Ariel A1, Serhan CN.
OMEGA-3 ACIDI GRASSI POLINSATURI (PFUA) E RISPOSTA ANTI-INFIAMMATORIA: LE PROTECTINE!

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Le PROTECTINE (PD1) E LE RISOLVINE (RvE3) POSSONO ESSERE FORMATE ANCHE DAGLI EOSINOFOILI: Emerging roles of eosinophils and eosinophil-derived lipid mediators in the resolution of inflammation!!
LE LIPOSSINE, LE RISOLVINE E LE PROTECTINE!!!

- EPA (eicosapentaenoic acid)
- DHA (docosahexaenoic acid)
LE LIPOSSINE, LE RISOLVINE E LE PROTECTINE!!!

DHA
docosahexaenoic acid

EPA
eicosapentaenoic acid
LE LIPOSSINE, LE RISOLVINE E LE PROTECTINE!!!

DHA
docosahexaenoic acid

EPA
eicosapentaenoic acid
LE LIPOSSINE, LE RISOLVINE E LE PROTECTINE!!!

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EPA
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LE LIPOSSINE, LE RISOLVINE E LE PROTECTINE!!!
LE LIPOSSINE, LE RISOLVINE E LE PROTECTINE!!!

DHA
docosahexaenoic acid

EPA
eicosapentaenoic acid
LE LIPOSSINE, LE RISOLVINE E LE PROTECTINE!!!
Recchiuti and Serhan

Resolving mechanisms in inflammation

FIGURE 3 | Biosynthetic schemes of SPM. (A) In humans, AA can be converted into 15S-H(p)-ETE through 15-LO and into 15R-H(p)-ETE by aspirin (ASA)-acetylated COX-2. Both intermediates can be further metabolized through 5-LO and enzymatic hydrolysis yielding LXA4 or 15-epi-LXA4.

(B) E-series resolvins are biosynthesized via conversion of EPA by ASA-acetylated COX-2. Products of these reactions, 18S-H(p)-EPE and 18R-H(p)-EPE, are rapidly taken up by 5-LO and converted to 18S-RvE1 and RvE1.

(C) The DHA metabolome includes several SPM biosynthesized via 15/5-LO and ASA-acetylated COX-2. Each SPM is biosynthesized via distinct biochemical routes involving stereocontrolled oxygenation, epoxide formation, and enzymatic hydrolysis. The main structures of key SPM and their biosynthetic routes (with precursors and main enzymes involved) are depicted (see text and Serhan and Petasis, 2011 for further details). The complete stereochemistry of each of these SPM is established, total organic synthesis achieved, and bioactions confirmed.

Chiral HPLC analysis indicated that the 18R-isomer was dominant to its epimer 18S-isomer in human plasma from healthy subjects taking EPA (Oh et al., 2011). In contrast, human subjects who were administered aspirin before EPA had more 18S- than 18R-HEPE, indicating that aspirin might promote 18S-HEPE production as well as 18R-HEPE from ingested EPA (Oh et al., 2011). This 18S-HEPE can also be converted to epimeric RvE1 and RvE2 by human recombinant 5-LO and LTA4 hydrolase (LTA4H), known as pro-inflammatory LTB4-synthesizing enzymes (Oh et al., 2011).

RvE1 is also produced in vivo through an aspirin-independent pathway via cytochrome P450-driven oxygenation of EPA (Serhan et al., 2000b). Of interest, RvE1 was also found to be produced by Candida albicans and appears to be involved in clearance of this organism (Haas-Stapleton et al., 2007). Thus RvE1 has multiple biosynthetic routes. RvE2 (5S,18-dihydroxy-EPE) is biosynthesized in resolving exudates and in human whole blood via reduction of 5S-hydroperoxy,18-hydroxy-EPE, an intermediate in the biosynthetic pathway of RvE1 (Tjonahen et al., 2006; Ogawa et al., 2009; Oh et al., 2012; Figure 3).

D-SERIES RESOLVINS

Earlier investigations using LC-MS/MS lipidomics of resolving exudates from mice given DHA and aspirin provided the first evidence of novel endogenous routes that lead to the formation of 17-hydroxy-containing mediators. Gaining information on how human tissue and cells may produce D-series Rv involved...
LA RISOLUZIONE DELL’INFIAMMAZIONE ACUTA!

British Journal of Pharmacology, 158, 960-97, 2009
Mediators and Receptors in the Resolution of Inflammation
LA RISOLUZIONE DELL’INFIAMMAZIONE ACUTA!

British Journal of Pharmacology, 158, 960-97, 2009
Mediators and Receptors in the Resolution of Inflammation
Table 2 | Resolvin, protectin, and maresin induced bioactions.

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<tr>
<td><strong>Resolvin E1</strong></td>
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<tr>
<td>Macrophages</td>
<td>Stimulates efferocytosis while reducing IFN-γ and IL-6 (Schwab et al., 2007)</td>
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<td>PMN</td>
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<tr>
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<tr>
<td><strong>Resolvin D1</strong></td>
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<tr>
<td>Microglia cells</td>
<td>Inhibits IL-1β expression (Serhan et al., 2002)</td>
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<td><strong>Protectin D1</strong></td>
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<tr>
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<td>Reduces IL-1β-induced NF-κB activation and COX2 expression (Marcheselli et al., 2003), reduces amyloid β-42-induced nerotoxicity, promotes amyloid β-induced apoptosis (Lukiw et al., 2005)</td>
</tr>
<tr>
<td>Epithelium</td>
<td>Protects from apoptosis induced by oxidative stress (Mukherjee et al., 2004)</td>
</tr>
<tr>
<td><strong>Maresin 1</strong></td>
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Different eicosanoids play pivotal roles in promoting inflammation and in its resolution.

Mediators and receptors in the resolution of inflammation.
Different eicosanoids play pivotal roles in promoting inflammation and in its resolution.
Resolution of inflammation TODAY!
Resolution of inflammation TODAY!

Maresins
I MEDIATORI LIPIDICI CHE RISOLVONO L’INFIAMMAZIONE OGGI SI DEFINISCONO Pro-resolving lipid mediators (SPMs) !!!

Pro-resolving lipid mediators (SPMs) !!!

Recchiuti and Serhan

Resolving mechanisms in inflammation

RE

SOLVING EXUDATES

("Pus bonum et laudabile")

LC-UV-MS-MS

Lipidomics

• Structure Elucidation
• Total Organic Synthesis
& Matching with Biogenic Compounds (H-NMR)

AA

EPA

Lipoxins E-series Resolvins

DHA

Maresins

SPECIALIZED PRO-RESOLVING LIPID MEDIATORS (SPM)

Serie A

Series B

Series D

- series Resolvins

A (Neuro)Protectins

Maresins

Fig. 2

B

• Mechanisms of Action
• S

A

R

D

•

FUNCTIONAL PROFILING OF SPM IN RESOLVING EXUDATES

(A) During self-limited inflammation, murine exudates (a "good and laudable" pus according to ancient physicians; Majno, 1991) as well as human leukocytes biosynthesize SPM, which include the lipoxins, E-series resolvins, D-series resolvins, protectins (neuroprotectin D1), and maresins, which work to keep the inflammatory response within physiological boundaries and help to expedite the return to homeostasis. Functional profiling takes advantage of liquid chromatography-ultraviolet spectrometry-tandem mass spectrometry (LC-UV-MS/MS) for identifying and quantifying SPM. Gas chromatography-mass spectrometry (GC-MS) is also useful to provide additional information together with LC-UV-MS/MS to support structural identification and proposed structures. Retrograde analysis with biogenic synthesis using isolated human cells and total organic synthesis allows the assignment of chirality and double bond geometries using H-NMR with synthetic materials and matching studies (see text; Fiore et al., 1991; Serhan et al., 2000a, 2002, 2006, 2012; Sun et al., 2007; Spite et al., 2009a; Krishnamoorthy et al., 2010 for details). Bioactions of SPM are assessed in both animal models and human cell systems. They must be stereoselective and evident at concentrations/doses that are commensurate with the amount of SPM produced.

(B) Example of RvD1 stereoselective total organic synthesis (reported in Sun et al., 2007); for further details (see Serhan and Petasis, 2011) for a recent review of organic synthesis.

To address the molecular basis for anti-inflammatory properties of ω-3 fatty acids, an unbiased LC-MS/MS-based informatics approach was developed to identify novel mediators generated from ω-3 precursors during acute inflammation in vivo. Using this approach, EPA and DHA were found to be enzymatically converted into novel potent LMs coined Rv, an acronym of resolution phase interaction products, because they: (a) are produced during cell–cell interactions occurring in the resolution phase of acute inflammatory response; (b) "stop" further neutrophil entry to sites of inflammation, and (c) reduce exudates (Serhan et al., 2000a, 2002, 2006; Hong et al., 2003; Bannenberg et al., 2005). Rv represented an entirely new family of mediators produced from the ω-3 fatty acids and importantly they appeared during the resolution phase via active biosynthetic processes. The biosynthesis of Rv gives rise to stereospecific local mediators that have potent actions and activate specific receptors.

E-SERIES RESOLVINS

EPA-derived E-series Rv are endogenously biosynthesized in vivo in resolving murine exudates and in isolated human cells systems by isolated cells (e.g., endothelial cell-leukocyte interaction) and in whole blood (vide infra). The complete stereochemistry of the first member of this family, RvE1, has been established as 5S,12R,18R-trihydoxy-6Z,8E,10E,14Z,16E-EPA (Arita et al., 2005a). For further details on the total organic synthesis (see Serhan and Petasis, 2011). Within vascular endothelial cells, aspirin-acetylated COX-2 converts EPA into 18R-hydro(peroxy)-eicosapentaenoic acid (HEPE), which is rapidly taken up by activated leukocytes (e.g., PMN) and further metabolized into RvE1. Notably, quantitative...
L’INFIAMMAZIONE PUÒ ESSERE CURATA CON L’ALIMENTAZIONE!

Since 1929, it has been established that omega-3 fatty acids are essential to health, and dietary deficiency can lead to disease (Burr and Burr, 1929).
ω-3 and ω-6 Polyunsaturated fatty acids (PUFA) are the major families of PUFA that can be found in human diet. After ingestion, both ω-3 and ω-6 PUFA are distributed to every cell in the body where they are involved in a myriad of physiological processes, including regulation of cardiovascular, immune, hormonal, metabolic, neuronal, and visual functions.

Dietary components and inflammation: ACIDI GRASSI POLINSATURI (PFUA)
Essi sono stati divisi in due classi note come omega 3 e 6, a seconda della posizione del primo doppio legame presente nella molecola. Gli omega 6 sono rappresentati dall’acido linoleico e dai suoi metaboliti (tra cui l’ac. arachidonico), mentre gli omega 3 sono rappresentati dall’acido alfa-linolenico e dai suoi metaboliti (ac. eicosapentaenoico, EPA, e ac. docosaesaeanoico, DHA).
According to the position of the first unsaturation, polyunsaturated fatty acids (PUFA) can be divided in omega 3 (n-3 PUFA; linolenic acid and its metabolites) and omega 6 (n-6 PUFA; linoleic acid). n-6 PUFA are precursors to AA and sustain production of pro-inflammatory eicosanoids (i.e. prostaglandins, leukotrienes). If n-3 PUFA are supplemented to the dietary, they can be incorporated into cell membranes and reduce the amount of AA available for the synthesis of proinflammatory eicosanoids. Furthermore, n-3 PUFA are converted in resolvins and protectins, thus contributing to their anti-inflammatory activity.

L’introduzione di quantità significative di omega 3 riduce la produzione di potenti mediatori infiammatori come le PGE delle serie 2, di citochine come TNF-alfa e IL-1 beta ed aumenta la produzione di risolvine e protectine e numerosi studi dimostrano che la supplementazione di olio di pesce (ricco di omega 3) migliora la sintomatologia di molteplici patologie infiammatorie e non.

Le patologie che in questo modo migliorano comprendono l'arteriosclerosi, la sclerosi multipla, la psoriasi, l'eczema, l'artrite reumatoide e molti altre di origine allergica/ infiammatoria.
Therapeutic potential of n-3 polyunsaturated fatty acids in disease

James W. Fetterman, Jr. and Martin M. Zdanowic

The potential therapeutic benefits of supplementation with n-3 polyunsaturated fatty acids (PUFAs) in various diseases are reviewed, and the antiinflammatory actions, activity, and potential drug interactions and adverse effects of n-3 PUFAs are discussed. SUMMARY: Fish oils are an excellent source of long-chain n-3 PUFAs, such as eicosapentaenoic acid and docosahexaenoic acid. After consumption, n-3 PUFAs can be incorporated into cell membranes and reduce the amount of arachidonic acid available for the synthesis of proinflammatory eicosanoids (e.g., prostaglandins, leukotrienes). Likewise, n-3 PUFAs can also reduce the production of inflammatory cytokines, such as tumor necrosis factor alpha, interleukin-1, and interleukin-6. Considerable research has been conducted to evaluate the potential therapeutic effects of fish oils in numerous conditions, including arthritis, coronary artery disease, inflammatory bowel disease, asthma, and sepsis, all of which have inflammation as a key component of their pathology. Additional investigations into the use of supplementation with fish oils in patients with neural injury, cancer, ocular diseases, and critical illness have recently been conducted. The most commonly reported adverse effects of fish oil supplements are a fishy aftertaste and gastrointestinal upset. When recommending an n-3 PUFA, clinicians should be aware of any possible adverse effect or drug interaction that, although not necessarily clinically significant, may occur, especially for patients who may be susceptible to increased bleeding (e.g., patients taking warfarin).

CONCLUSION: The n-3 PUFAs have been shown to be efficacious in treating and preventing various diseases. The wide variation in dosages and formulations used in studies makes it difficult to recommend dosages for specific treatment goals.
The bioactive lipid mediators in inflammation activation and resolution!

The precursor ω-6 fatty acid AA and the ω-3 fatty acids eicosapentaenoic acid (EPA) and DHA can generate a range of both proinflammatory and anti-inflammatory lipid mediators via actions of LO, COX-2, or aspirin-acetylated COX-2 enzymes. AA forms a range of proinflammatory mediators, such as the prostaglandins (PGs), via COX-2, and the leukotrienes (LTs), via multiple LO action. An array of anti-inflammatory and proresolving mediators, including resolvins, protectins, and maresins, is generated from EPA and DHA by LO. The 13-electrophilic oxo derivative (EFOX) is formed by COX-2 action, although its anti-inflammatory properties have only been documented in vitro (distinguished from other lipid mediators by a dashed line). In the presence of aspirin, acetylated COX-2 generates an epimeric range of ATLs, resolvins, protectins, and an alternative 17-EFOX product.
n−3 PUFAs modulate T cell activation!

Omega-3 Fatty Acids Prevent Inflammation and Metabolic Disorder through Inhibition of NLRP3 Inflammasome Activation!

Immunity, 38,6,p1154–1163, 27, 2013

n−3 PUFAs increase lipid raft molecular order and suppress the recruitment and activation status of signaling proteins in the CD4+ T cell synapse. T cell activation results in an increase in lipid raft molecular order following the formation of the T cell – antigen presenting cell dependent immunological synapse. Green circles indicate cholesterol-enriched liquid ordered domains, which stabilize at the immunological synapse. Red circles indicate n−3 PUFA-dependent suppression of lipid second messengers (PIP2, DAG) and proteins (PLC-1, PKCθ, F-actin, NF-kB) required for T cell activation. APC, antigen presenting cell.

Prostaglandins Leukot Essent Fatty Acids. 2010 Apr-Jun;82(4-6):179-87
Omega-3 PUFAs modulate T cell activation!

$n$-$3$ PUFAs increase lipid raft molecular order and suppress the recruitment and activation status of signaling proteins in the CD4$^+$ T cell synapse. T cell activation results in an increase in lipid raft molecular order following the formation of the T cell – antigen presenting cell dependent immunological synapse. Green circles indicate cholesterol-enriched liquid ordered domains, which stabilize at the immunological synapse. Red circles indicate $n$-$3$ PUFA-dependent suppression of lipid second messengers (PIP$_2$, DAG) and proteins (PLC-$1$, PKC$_{\theta}$, F-actin, NF-$k$B) required for T cell activation. APC, antigen presenting cell.

Omega-3 Fatty Acids Prevent Inflammation and Metabolic Disorder through Inhibition of NLRP3 Inflammasome Activation!

Immunity, 38,6,p1154–1163, 27, 2013

NEW: GLI OMEGA 3 MODULANO L’ATTIVAZIONE DEI LINFOCITI T E L’INFLAMMASOMA!

Prostaglandins Leukot Essent Fatty Acids. 2010 Apr-Jun;82(4-6):179-87
GLI OMEGA 3 PREVENGO IL RIASSORBIMENTO OSSEO!
DIET, BONE LOSS AND THE IMMUNE SYSTEM!!!!!!

INHIBITION OF PRO-INFLAMMATORY CYTOKINES SUCH AS IL-1, IL-6, TNF-alfa, GM-CSF, AND PROSTAGLANDIN E2 WHICH INCREASE OSTEOCLAST PROLIFERATION!
The anti-inflammatory actions of the omega-3 fatty acids are now recognized to be at least partly mediated by cell surface and intracellular receptors, GPR120 and NR1C3 (i.e. PPAR-γ).

Summary of the anti-inflammatory actions of marine n-3 polyunsaturated fatty acids. ARA, arachidonic acid; COX, cyclooxygenase; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GPR, G-protein coupled receptor; iNOS, inducible nitric oxide synthase; MMP, matrix metalloproteinase; NFκB, nuclear factor kappa B, PPAR, peroxisome proliferator activated receptor. Dotted lines indicate inhibition.
Omega-3 polyunsaturated fatty acids immune relevance!
Gli omega-3 regolano la risposta immunitaria attraverso le resolvine, le protectine e le maresine che riducono l'infiammazione bloccando l'infiltrazione dei neutrofili, promuovendo l'eliminazione delle chemochine infiammatorie, e migliorando la fagocitosi dei macrofagi per eliminare cellule apoptotiche!
Gli omega-3 regolano la risposta immunitaria attraverso le resolvine, le protectine e le maresine che riducono l'infiammazione bloccando l'infiltrazione dei neutrofili, promuovendo l'eliminazione delle chemochine infiammatorie, e migliorando la fagocitosi dei macrofagi per eliminare cellule apoptotiche!

Modelli animali suggeriscono anche che gli omega-3 modulano l'infiammazione attivata da TLR2 e TLR4!
Gli omega-3 regolano la risposta immunitaria attraverso le resolvine, le protectine e le maresine che riducono l'infiammazione bloccando l'infiltrazione dei neutrofili, promuovendo l'eliminazione delle chemochine infiammatorie, e migliorando la fagocitosi dei macrofagi per eliminare cellule apoptotiche!

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Modelli animali suggeriscono anche che gli omega-3 modulano l’infiammazione attivata da TLR2 e TLR4!

Un potente fattore dietetico che modula la risposta infiammatoria/immunitaria può essere il maggiore consumo di acidi grassi omega-6 al posto di acidi grassi omega-3!

L’INFIAMMAZIONE ACUTA E LA RISPOSTA IMMUNITARIA INNATA SONO BLOCCATE E CONTROLLATE DA CITOCHINE ANTI-INFIAMMATORIE!

IL1RA
IL10
TGF beta

QUESTE CITOCHINE SONO I MARCATORI DELLA RESOLUZIONE DELL’INFIAMMAZIONE!
Acute inflammation activation and resolution and associated **CYTOKINE** mediators!

**Onset**
- Exudation
- Neutrophils
- Apoptosis
- Mononuclear cells

**Resolution**

<table>
<thead>
<tr>
<th>Time</th>
<th>30min</th>
<th>1h</th>
<th>3h</th>
<th>6h</th>
<th>24h</th>
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</thead>
<tbody>
<tr>
<td><em>Histamine</em></td>
<td>Substance P</td>
<td>TNF</td>
<td>MCP1</td>
<td><em>IL1RA</em></td>
<td><strong>IL10</strong></td>
</tr>
<tr>
<td><em>Serotonin</em></td>
<td>PAF</td>
<td><strong>IL-1β</strong></td>
<td>IL-6</td>
<td><strong>TGF beta</strong></td>
<td></td>
</tr>
<tr>
<td><em>Bradykinin</em></td>
<td>PGs</td>
<td><strong>IL-8/KC</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Complement</em></td>
<td>LTs</td>
<td>LXs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**LIPOXINS, RESOLVINS, PROTECTINS, MARESINS**
Polarization of Tumor-Associated Macrophages during tumor progression

Macrophage production of immunosuppressive cytokines at late timepoints after LPS stimulation

Balance of cytokine action determines severity of inflammation

Activating factors:
- TLR
- ImmR
- IFNγR
- Stat1

Suppressive factors:
- TGFβ
- IL-10 (Stat3)
- IL-1RA

Espressione of cytokines:
- TNF
- IL-1
- IL-6
- IL-10
- TGFβ
In the inflammation resolution, macrophages M2 produce the soluble IL-1 receptor antagonist (IL-1ra)!

A family of IL-1 receptors!

The expression of different receptor molecules and of signalling modulators is regulated!

**IL-1 RI**: functional receptor  
**IL-1 RII**: “decoy” receptor  
**IL-1ra**: soluble receptor antagonist  
**IL-1RAcP**: accessory protein for IL-1 RI and IL-1 RII

**Tollip**: inhibitor of IL-1R signalling pathway
Anakinra: soluble IL-1 receptor antagonist (IL-1ra) as a therapy for gout!!!!

Model of the role of IL-1β and NALP3 inflammasome in gouty inflammation

---

Figure 1: Model of the role of IL-1β in gouty inflammation. MSU crystals internalized by monocytes activate the NALP3 inflammasome (Phase 1, lower left). NALP3 protein activation leads to the recruitment and activation of the adaptor ASC and caspase-1 via PYD-PYD and CARD-CARD homotypic interactions, resulting in the processing and maturation of pro-IL-1β into its biologically active form, IL-1β. IL-1β (mainly acting on nonleukocytic cell types, possibly synoviocytes) will then activate the IL-1R complex, leading to recruitment of MyD88 via TIR-TIR homotypic interactions. This results in the activation of NF-κB, which will turn on the transcription of neutrophil-recruiting chemokines, such as IL-8, S100, or macrophage inflammatory protein 2 (MIP-2) (Phase 2, lower right). ASC, apoptosis-associated speck-like protein containing a CARD; CARD, caspase-recruitment domain; DD, death domain; PYD, pyrin domain.
In the inflammation resolution, macrophages M2 produce IL-10!

IL-10 is an anti-inflammatory cytokine!

Cytokine signaling modules in inflammatory responses.

Mechanisms Associated with Socs3-Mediated Suppression of Anti-inflammatory Signaling by the IL-6R
Transforming growth factor-β (TGF-β) has been considered an anti-inflammatory cytokine responsible for the bland removal of apoptotic cells. To date both decreased (favoring predominance of inflammation) and increased (favoring resolution of inflammation but potentially pro-fibrotic) responses have been demonstrated.

Clearance of apoptotic cells: TGF-β in the balance between inflammation and fibrosis
Robert M. Clancy and Jill P. Buyon

The inflammatory response and cardiac repair after myocardial infarction.
Nah DY, Rhee MY.
L’INFIAMMAZIONE ACUTA E LA RISPOSTA IMMUNITARIA INNATA SONO BLOCCATE E CONTROLLATE DA PENTRAXINE!

LE PENTRAXINE CHE BLOCCANO L’INFIAMMAZIONE E LA RISPOSTA IMMUNITARIA INNATA SONO LE PTX3!
PTX3, un freno all’infiammazione!

Un recente studio pubblicato su "Nature Immunology" e coordinato dal gruppo del prof. Alberto Mantovani chiarisce il meccanismo alla base della funzione di regolazione dell'infiammazione svolta dalla proteina PTX3 e apre a nuovi sviluppi per l'utilizzo diagnostico e terapeutico di questa molecola.

La ricerca ha dimostrato che la PTX3 svolge la propria funzione nella fase infiammatoria interagendo con un'altra proteina, la P-selettina, espressa dalle cellule endoteliali in presenza di uno danno tissutale o di uno stimolo infiammatorio. Mediante l'interazione con la P-selettina, la PTX3 rallenta e limita l'infiltrazione dei leucociti nel sito infiammato, agendo localmente per ridurre il loro reclutamento e regolando in tal modo la risposta infiammatoria. Si tratta di una scoperta che avvicina in maniera significativa la possibilità dell'utilizzo clinico della molecola.

Regulation of leukocyte recruitment by the long pentraxin PTX3
“Nature Immunology”, published online 7 March 2010; doi:10.1038/ni.1854
LA RISPOSTA INFIAMMATORIA ED IMMUNITARIA È CONTROLLATA INFINE DAL SISTEMA NEUROENDOCRINO!

Ormoni e circuiti del sistema nervoso che controllano l’infiammazione ed il sistema immunitario!
Inflammatory products produced in damaged tissues activate afferent signals that are relayed to
the nucleus tractus solitarius. Subsequent activation of vagus efferent activity inhibits cytokine
synthesis through the activation of a cholinergic anti-inflammatory pathway ('the inflammatory
reflex') mediated by signals delivered by the $\alpha_7$ subunit of the AChR on macrophages.
The inflammatory reflex controls innate immune responses by targeting NF-κB (and cytokine receptor signalling)

Stranger & danger signals

Exogenous ligands
- Lipopolysaccharide
- Lipoteichoic acid
- CpG-containing DNA
dsRNA
- Haemozoin
- Flagellin

Endogenous ligands
- HMGB1
- Heat shock proteins
- Uric acid
- IL-1β
- Annexins
- Nucleolin

TNF, IL-1β

TLR

NLR

NF-κB

Pro-inflammatory cytokines

Cytoplasm

Nucleus

Brain

Spleen

Afferent arc

Efferent arc

Acetylcholine

α7nAChR

Glioblastoma
Cytokines produced by immune cells in response to endogenous and exogenous stimuli activate afferent neurons of the vagus nerve that conveys this information to the brain where signal integration occurs. A response is elicited through the cholinergic anti-inflammatory pathway, the efferent arc of this inflammatory reflex, which modifies immune function and maintains homeostasis. The cholinergic anti-inflammatory pathway conveys signals from the brain to the spleen via the vagus nerve and the splenic nerve and is dependent on the α7 subunit of the nicotinic acetylcholine receptor.
The crosstalk between immune system and autonomic nervous system regulates inflammation.
The crosstalk between immune system and autonomic nervous system regulates inflammation

(a) Adrenergic pro-inflammatory pathway
- Release of catecholamines from adrenal medulla, sympathetic neurons, phagocytic cells and lymphocytes
- Catecholamine
- Adrenergic receptor
- Macrophage
- Increased release of pro-inflammatory mediators
- Amplified inflammatory response

(early)

(b) Cholinergic anti-inflammatory pathway
- Vagus-nerve stimulation
- Release of acetylcholine (or $\alpha_2$-nAChR agonists)
- Acetylcholine
- $\alpha_2$-nAChR
- Decreased release of pro-inflammatory mediators
- Suppressed inflammatory response
The crosstalk between immune system and autonomic nervous system regulates inflammation.
The crosstalk between immune system and autonomic nervous system regulates inflammation.

The inflammatory reflex!

Cateolamines

(early)
NON SOLO LE CITOCChINE INFiammatorie,
MA ANCHE LA RISPOSTA INFiammatoria E QUELLA IMMUNITARia SONO CONTROLLATE DAL SISTEMA NEUROENDOCRINO!
Anche i glucocorticoidi, come il cortisolo, inibiscono la risposta infiammatoria!

Down-regulation of inflammatory responses by glucocorticoid hormones!

Glucocorticoid hormones suppress the production of pro-inflammatory cytokines!
I glucocorticoidi, come il cortisolo, inibiscono tutta la risposta immunitaria!

**Effects of glucocorticoids on immune cell populations!**

Figure 2 | Effects of glucocorticoids on immune-cell populations. Glucocorticoids act on immune cells both directly and indirectly to suppress the induction of pro-inflammatory responses. They inhibit the production of pro-inflammatory cytokines, such as interleukin-1β (IL-1β) and tumour-necrosis factor (TNF), while promoting the production of anti-inflammatory cytokines, such as IL-10, by macrophages and dendritic cells. They also promote apoptosis of macrophages, dendritic cells and T cells, leading to inhibition of immune responses. IFNγ, interferon-γ; NK cell, natural killer cell; T_C, cytotoxic T cell; T_H, T helper cell.
Local and systemic anti-inflammatory reflexes

The hypothalamic–pituitary–adrenal axis is activated by:
• nociceptive pathways (SNS)
• vagus stimulation
• systemic pro-inflammatory cytokines (BBB leakage)
Neuroendocrine Afferent and Efferent Pathways Restore Homeostasis after INFLAMMATION!
The bidirectional communications between the hypothalamic-pituitary axes, the nervous system, and the immune system are INCREDIBLE!!!

Hormones released by the adrenals and gonads, such as glucocorticoids and progesterone, respectively, work in parallel with neurotransmitters and neuropeptides to regulate the immune system. In turn, cytokine signaling provides stimulus or feedback to the hypothalamus to regulate the hormonal and neuronal response.

Dotted lines represent negative regulatory pathways, and solid lines represent positive regulatory pathways.

- A1, C1, A2, C2, Brainstem adrenergic nuclei;
- Vagus n., vagus nerve;
- LC, locus ceruleus;
- PNS, peripheral nervous system;
- SNS, sympathetic nervous system;
- ACTH, adrenocorticotrophin hormone;
- AVP, arginine vasopressin;
- CRH, corticotrophin-releasing hormone;
- DHEA, dehydroepiandrosterone;
- FSH, follicle-stimulating hormone;
- GnRH, gonadotropin-releasing hormone;
- LH, luteinizing hormone;
- T3, tri-iodothyronine;
- T4, thyroxine;
- TRH, thyrotropin-releasing hormone;
- TSH, thyroid-stimulating hormone;
- Glucocorticoids (Cortisol, etc);
- NGF, nerve growth factors;
- Catecolamine;
- Neuropeptides (Substance P, etc.)
- Leptin
Substance P (SP) leads to many of the typical features of asthmatic inflammation in the airway, including eosinophil and mast cell activation and degranulation, mucus cell hypersecretion and smooth muscle contraction. SP induces proinflammatory cytokine secretion from inflammatory and epithelial cells in the airway, which amplifies local inflammation.
Examples of efferent nerve pathways that modulate mast cell function! 

Mast cells: proximal mediators within the hierarchical stress-response network in skin inflammation. Upon stress exposure, CRH and NGF are increasingly present in the skin, either in the hair follicle, or secreted by activated mast cells upon stimulation by them or by CGRP or NT. Proteases such as tryptase secreted by activated mast cells induce the release of inflammatory neuropeptides, for example SP, via PAR-dependent pathways, resulting in an autocrine and/or paracrine mechanism of mast-cell activation with subsequent NGF production besides other inflammatory cytokines (TNF) or vasodilatory molecules (VEGF). Both TNF and NGF might also induce apoptosis, which then diminishes stem cells residing in the bulge area.
It is clear that important communications among the immune system, the nervous system and the hypothalamic–pituitary–adrenal axis are mediated by:

- The inflammatory reflex!
- Catecolamines
- Glucocorticoids (cortisol)
- NGF
- Neuroptides (SP)
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!

The cholinergic anti-inflammatory pathway: The inflammatory reflex!
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!

Glucocorticoid hormones!

The cholinergic anti-inflammatory pathway: The inflammatory reflex!
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!

Glucocorticoid hormones!

The cholinergic anti-inflammatory pathway: The inflammatory reflex!

CATECOLAMINS!

NGF!

SUSTANCE P!
NEW IMMUNOMODULATING FACTORS: THE LEPTIN CASE!
Leptin was first characterized as a hormone that plays a central role in the control of body adiposity!

A number of studies later revealed several other functions for leptin, including the capacity to modulate immune system activity. Under certain environmental conditions, insufficient or excessive food consumption leads to pathological adiposity and, therefore, to anomalous leptin production. In malnutrition, leptin levels are extremely low as are its functions. Currently, leptin occupies an important position as a unifying mechanism integrating nutritional status and immune function.

Effects of recombinant human leptin treatment in a patient with congenital leptin deficiency.

(A) Before treatment.
(B) After treatment.

Leptin at 14 y of age: an ongoing story.
Friedman JM.
Is leptin the link between nutrition and immunity?

**Brain**
- Increases basal metabolism
- Modulates reproductive function
- Modulates pancreatic, T-cell function

**Thymus**
- Proliferation, A52
- T-cell receptor expression

**Lymph Nodes**
- T-cell activation

**Adipose Tissue**
- Leptin production

**Leptin**
- Modulates immune function
- Lipolysis

**References**
- Howard J, Lord G & Matarese G et al, JCI, 1999
La leptina controlla le funzioni del timo!
La leptina controlla le funzioni del timo!
La leptina controlla le funzioni del timo!

Putative hormonal circuit involved in triggering the depletion of thymocytes that occurs in malnourished individuals. Accordingly, in physiological conditions, there is a balance (herein illustrated by the Chinese Ying-Yang symbol of equilibrium) between glucocorticoids (pro-apoptotic) and leptin (anti-apoptotic) levels, accounting for the normal pattern of thymocyte apoptosis. In malnutrition, there is a decrease in leptin levels, leading to a stimulation of the hypothalamus–pituitary–adrenal axis that results in increased circulating levels glucocorticoid hormones, which in turn enhance thymocyte apoptosis. As indicated by the arrows, this situation can be reversed by the re-establishment of an appropriate diet.

The thymus gland is a target in malnutrition.

W Savino
Table 1

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Lep receptor</th>
<th>Leptin effects on cell function</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monocytes/macrophages</td>
<td>Yes</td>
<td>Up-regulates phagocytic function; up-regulates proinflammatory cytokine secretion (TNF-α, IL-6, IL-12) and the expression of activation markers; increases cell motility.</td>
<td>Direct</td>
</tr>
<tr>
<td>Dendritic cells</td>
<td>Yes</td>
<td>Promotes survival; increases immature DC migratory performance and the stimulatory capability of allogenic T cells.</td>
<td>Direct</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>Unknown</td>
<td>Induces chemotaxis and the release of oxygen radicals</td>
<td>Indirect</td>
</tr>
<tr>
<td>NK cells</td>
<td>Yes</td>
<td>Increases the expression of activation marker (CD69); sustains cytotoxic activity and perforin production.</td>
<td>Direct</td>
</tr>
<tr>
<td>B cells</td>
<td>Yes</td>
<td>Increases lymphopoiesis and maturation; induces secretion of cytokines, such as IL-6, IL-10, and TNF-α; increases IgG2a production.</td>
<td>Direct</td>
</tr>
<tr>
<td>T cells</td>
<td>Yes</td>
<td>Induces the expression of activation markers; increases proliferation of naïve T cells; promotes the switch towards Th1-cell immune responses by increasing IFN-γ and TNF-α secretion; increases the expression of adhesion molecules; promotes the survival of thymic T cells.</td>
<td>Direct</td>
</tr>
<tr>
<td>Regulatory T cells</td>
<td>Yes</td>
<td>Constrains their proliferation and suppressive activity, through the activation of the mTOR pathway.</td>
<td>Direct</td>
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Mice lacking leptin or its functional receptor have a number of defects in both cell-mediated and humoral immunity ([Mandel and Mahmoud, 1978](#)). Similarly, humans with congenital leptin deficiency have a much higher incidence of infection-related death during childhood ([Ozata et al., 1999](#)), whereas recombinant human leptin (rmetHuLeptin) administration in two children with congenital leptin deficiency normalized absolute numbers of naïve CD4+CD45RA+ T cells and nearly restored the proliferation response and the cytokine release profile from their lymphocytes ([Farooqi et al., 2002](#)). A number of studies in mice have shown that the effect of leptin on the immune system is both direct and indirect, i.e., via modulation of central or peripheral pathways ([Fraser et al., 1999](#) and [Zhang et al., 2002](#)).
In normal subjects, secretion of adipocyte-derived leptin associates with a normal control of metabolic functions and with a balance between the number of Th1 cells and Th2/Treg cells, which are functionally able to suppress immune and autoimmune responses. Indeed leptin contributes to protection from infectious agents, on the one hand, but also, to loss of tolerance and autoimmunity, on the other hand. Reduction of the level of circulating leptin [e.g. owing to protein-energy malnutrition (PEM), anorexia nervosa or genetic leptin deficiency (ob/ob)] results in impaired Th1 response and induction of Treg cells, thus reducing the immunocompetence in humans and mice and increasing susceptibility to infection. Conversely, the high amount of leptin secreted by adipocytes [e.g. obesity or genetic leptin-receptor deficiency (db/db)], accounts for an altered control of metabolic functions, often associated with insulin-resistance, a high frequency and expansion of Th1 cells and increased secretion of pro-inflammatory cytokines, on one side, and a low proportion and proliferation of Treg cells infiltrating adipose tissue, on the other. Along with the increased numbers of Th1 cells in adipose tissue, higher number of CD8$^+$ T cells, macrophages and mast cells have been reported. Excess of leptin levels may lead to the establishment of a condition of leptin resistance (which is strongly connected to obesity development). In this condition, obese individuals also more susceptible to infectious diseases. Moreover, recent evidence has highlighted the central role of central leptin signaling in the control of immune system, thus suggesting that the central nervous system (CNS), via peripheral nervous system (PNS), is able to directly modulate immune function.

Leptin as an immunomodulator.
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!

The cholinergic anti-inflammatory pathway: The inflammatory reflex!
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!

Glucocorticoid hormones!

The cholinergic anti-inflammatory pathway: The inflammatory reflex!
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Glucocorticoid hormones!

The cholinergic anti-inflammatory pathway: The inflammatory reflex!

CATECOLAMINS!
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!
Connections between the nervous, endocrine and immune systems: a SUPERSYSTEM!!!
Akin to the classic map of the brain that identifies which neural networks regulate or coordinate specific actions in the periphery, it is possible that additional research may identify that specific regions of the brain control other immune responses, potentially via the inflammatory reflex and its efferent arm, the cholinergic, anti-inflammatory pathway, as depicted in this pictorial hypothesis.
The immunological homunculus. The CNS is organized somatotopically, such that specific neural networks regulate or coordinate particular actions in the periphery. Advances in neuroimaging and neuroscience have made it possible to study this neural organization in humans. Knowledge about the cholinergic antiinflammatory pathway as a specific regulator of cytokine responses makes it possible to consider whether there is somatotopic organization to CNS regulation and coordination of the behavior of the immune system. It is plausible that this control extends beyond the simple regulation of cytokines. In the future, it may be possible to map specific brain regions that control other immune responses as depicted in this artistic rendition.
LA PERSISTENTE ED INAPPROPRIATA ATTIVAZIONE DEL SISTEMA IMMUNITARIO E DALLA RISPOSTA INFIAMMATORIA PUÒ INDURRE DEPRESIONE!!!!!!

Acute and chronic immune and inflammatory processes, combined with relevant contributions from immunogenetics (such as polymorphisms in cytokine genes) and past immune experiences (such as prior infections and vaccination history) (orange) interact with acute and chronic stressors combined with relevant contributions from psychiatric genetics (such as polymorphisms in neurotransmitter transporter genes) and past emotional experiences (such as adversity in early life) (yellow) to promote the syndrome of major depression (brown). A diagnosis of major depression is based on the presence of five of the following symptoms: depressed mood, anhedonia, fatigue, guilt and/or worthlessness, suicidal ideation, impaired concentration and/or memory, psychomotor retardation and/or agitation and disturbances of sleep or appetite. Symptoms must persist for at least two weeks and cause significant functional impairment...
LO STRESS ED UNA DISREGOLATA ATTIVAZIONE DEL SISTEMA IMMUNITARIO E DELLA RISPOSTA INFIAMMATORIA POSsono INDURRE DEPRESSIONE!!!!!!!
acute and chronic stressors + relevant genetic background + past emotional experiences

acute and chronic immune and inflammatory processes + relevant genetic background
The inflammatory and immune response, and ways of controlling it.....
Health: Edible advice.
Ahmed F.
......including nutrition..

Health: Edible advice.
Ahmed F.
Health: Edible advice.
Ahmed F.
......and laughter (buon umore)!

Chronic inflammatory disorders

Pharmacological agents
- Acupuncture
- Electrical stimulation
- Nicotine
....and laughter (buon umore)!

LAUGHTER

Pharmacological agents

Acupuncture
Electrical stimulation
Nicotine

Chronic inflammatory disorders

Sensory vagus nerve
Interleukin-1 receptor
Interleukin-1
TNF
Acetylcholine
α7 receptor
Cytokine protein
Cytokine messenger RNA
Invading microorganism (lipopolysaccharide)

Brain
Effenter vagus nerve
Macrophage
Beginning of the history of studies on laughter


Research on the subject of laughter commenced during the 20th century. The first paper that reported the relationship between laughter and health was authored by Norman Cousins, who cured himself of a disease with laughter. He was diagnosed with ankylosing spondylitis. He reviewed his living conditions during the onset of the disease; thereafter, considering overfatigue or negative stress to be the cause underlying the disease, he assumed that laughter—as a form of expression of positive emotion—would favorably affect health. Consequently, he practiced laughter to aid his recovery. He found that laughter allowed him to enjoy painless sleep and lowered the sedimentation rate to a certain extent.

After several months, he successfully recovered from the disease!
Bibliography of studies on laughter

Leiber DB. Laughter and humor in critical care. Dimens Crit Care Nurs 1976;5:


The laughter benefits have been reported in geriatrics, oncology, critical care, psychiatry, rehabilitation, rheumatology, home care, palliative care, hospice care, terminal care, and general patient care, as suggest by one comprehensive paper on laughter!

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Laughter prescription

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One area where questions remain are the biological and molecular mechanisms of the effect of laughter!

It has been demonstrated that laughter modulates inflammation and the function of the immune system!
Le catecolamine come ormoni sono rilasciate dalle ghiandole surrenali in situazioni di stress come stress psicologico o cali di glicemia. Le catecolamine più importanti sono l'adrenalina (epinefrina), la noradrenalina (norepinefrina) e la dopamina.
Examples of efferent nerve pathways that modulate mast cell function!

Mast cells: proximal mediators within the hierarchical stress-response network in skin inflammation. Upon stress exposure, CRH and NGF are increasingly present in the skin, either in the hair follicle, or secreted by activated mast cells upon stimulation by them or by CGRP or NT. Proteases such as tryptase secreted by activated mast cells induce the release of inflammatory neuropeptides, for example SP, via PAR-dependent pathways, resulting in an autocrine and/or paracrine mechanism of mast-cell activation with subsequent NGF production besides other inflammatory cytokines (TNF) or vasodilatory molecules (VEGF). Both TNF and NGF might also induce apoptosis, which then diminishes stem cells residing in the bulge area.
In experiments that measured the concentration of the factors produced by the neuroendocrine system in subjects before and after watching a 60-min comedy video it was observed that the blood cortisol level (stress index) continued to decrease during the video show. (Berk et al. 1989)
DIMINUZIONE DELLA PERCEZIONE DEL DOLORE, indotto da SOSTANZA P, BRADICHININA E PROSTAGLANDINA I2 (PGI2)!

IL BUON UMORE (LAUGHTER), DIMINUENDO LO STRESS, DIMINUISCE IL RILASCIO DELLA SOSTANZA P!

DIMINUZIONE DELLA PERCEZIONE DEL DOLORE, indotto da SOSTANZA P, BRADICHININA E PROSTAGLANDINA I2 (PGI2)!

PAIN !!!
“Laughter is the tonic, the relief, the surcease for pain”.

Charlie Chaplin