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Alternative activation of macrophages: mechanisms and functions - Evidence review

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1. ABSTRACT

The analyzed publication is a narrative review dedicated to the alternative activation of macrophages, innate immune cells capable of changing their behavior in response to environmental signals. In particular, it examines the effects of the cytokines interleukin-4 and interleukin-13, signals produced primarily during T helper 2-type responses. Since only the abstract is available, no sample, quantitative experimental procedures, or original numerical results are reported.In section 6.1 of “The Choice to Live in Health or Illness” by Dr. A. Colonnese and R. Panzironi, the publication contributes to the description of macrophages as cells that, in addition to engulfing pathogens, release cytokines capable of recruiting other immune cells and regulating the intensity of the response. Independent studies show that macrophages can produce signals that promote neutrophil recruitment and that communication between immune cells modifies the quantity and type of cytokines released. The evidence therefore supports the general concept, but it is derived primarily from cell cultures and animal models, not from targeted clinical studies.

ONLINE ARTICLE

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MISSION

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Through articles, reviews, in-depth analyses and expert contributions, the Journal champions evidence-based medicine and science, fostering a correct interpretation of scientific data and countering misinformation. Every piece of content is developed with the aim of translating the complexity of research into understandable, useful and applicable information, while keeping intact the principles of accuracy, transparency and scientific independence.

Free from political, industrial and commercial influence, the journal stands as an authoritative and independent editorial space, dedicated to promoting scientific culture, professional development and the growth of health awareness among the public.

2. ANALYZED STUDY

The question addressed by the publication is how to define alternative macrophage activation and what functions these cells assume when they receive specific immune signals. Macrophages are cells that recognize, engulf, and degrade microbes, damaged cells, and other materials; at the same time, they produce signaling molecules that influence neighboring cells.The publication focuses primarily on the action of interleukin-4 and interleukin-13, two cytokines—small proteins used by cells to transmit instructions. The authors discuss how these signals modify macrophage biology and propose a more precise definition of "alternative activation." In this section of the book, however, the relevant function is not the entire biology of alternative activation: it is the role of macrophages as cells that release chemical signals capable of directing and modulating an immune response.As this is a narrative review and not a single experiment, the study analyzed can integrate previous knowledge and propose an interpretive framework. It cannot, on its own, causally demonstrate in humans that a particular cytokine produced by a macrophage determines the overall intensity of the immune response in every tissue or disease.

3. MATERIALS AND METHODS OF THE ORIGINAL STUDY

The publication is a narrative review of the scientific literature on the alternative activation of macrophages. The available abstract indicates that the authors evaluated recent research, discussed a narrow definition of the phenomenon, and explored the pathways through which interleukin-4 and interleukin-13 influence macrophage cell biology.No participant recruitment is described, no sample size is reported, and there is no unique experimental control group, as the work does not present an original experiment. The bibliographic search criteria, the databases consulted, the period covered, the study inclusion criteria, the statistical analyses, and the formal assessment of the risk of bias are not reported in the available material.

4. RESULTS

The central finding is conceptual: T helper 2 cytokines, particularly interleukin-4 and interleukin-13, can modify macrophage behavior and direct them toward a program defined by the authors as alternative activation.For the purpose of this book, it is relevant that the publication recognizes that macrophages have a regulatory function in addition to phagocytosis, that is, beyond the engulfment of microorganisms or cellular debris. The cytokines released or perceived by macrophages actually contribute to communication between immune cells and can promote inflammatory responses, limit certain signals, or support repair processes.The available material does not allow for the attribution of direct experimental data to the publication regarding the recruitment of specific immune cells, nor does it allow for quantifying the extent to which macrophage cytokines modify the response in healthy or sick individuals.

5. INTERPRETATION

In common parlance, macrophages are not just cells that eliminate what can harm the body. They are also cells that send messages: these messages can attract other defenses to the site where they are needed and help make the response more intense, more localized, or more focused on repair.The segment of the narrative documented by the publication subject to the Evidence Review is therefore: macrophages exposed to signals from the immune environment functional change in macrophages production of or response to cytokines modulation of immune communication. Alternative activation mediated by interleukin-4 and interleukin-13 represents an example of this plasticity, that is, the ability of the same cell to adopt different functional programs.This interpretation does not mean that every macrophage can be clearly classified as M1 or M2, nor that a single cytokine alone determines the entire immune response. Functions depend on the tissue, the type of stimulus, the timing of the response, and interactions with other cells.

6. INDEPENDENT CONFIRMING EVIDENCE

Experimental confirmation of the step involving the recruitment of other immune cells comes from a study

in mice with peritoneal inflammation induced by lipopolysaccharide, a component of the cell wall of certain bacteria. Researchers observed that tissue macrophages produced CXCL1 and CXCL2, which are chemokines—cytokines specialized in guiding cell movement. When macrophages were experimentally reduced, neutrophils still exited the blood vessels but reached the peritoneal fluid less effectively. This result causally supports, in the mouse model, that signals produced by macrophages contribute to the local recruitment of other immune cells [1]. The limitation is that the model concerns acute inflammation in mice and does not directly measure a human clinical response.A second study analyzed fresh human monocytes and cells differentiating into macrophages following stimulation of Toll-like receptors, which are sensors that recognize microbial components. Activation of these receptors induced the production of CCL1, CCL2, and CCL4; furthermore, the culture medium containing the substances released by the cells showed a different capacity to attract blood mononuclear cells. This links the variation in chemokine production to a variation in the migration of other immune cells [2]. This is a confirmation biologically close to the statement in the book, but it was obtained in the laboratory and, crucially, in monocytes rather than in infected human tissue.A third study showed that macrophages do not release cytokines as simple isolated cells: the cytokines produced by some cells influence other cells in the same population. In human monocyte-derived macrophages and in a macrophage cell line, cell isolation reduced the lipopolysaccharide-induced secretion of interleukin-6 and interleukin-10. The signal from tumor necrosis factor-alpha, or TNF-alpha, produced by a small fraction of cells, was necessary but not sufficient for high production of interleukin-6 and interleukin-10 [3]. The study confirms that cytokines participate in regulating the intensity and quality of the response, but it does not demonstrate that the same circuit operates identically in all organs or in chronic diseases.

7. CONFLICTING EVIDENCE

No directly conflicting evidence of sufficient relevance has been identified; this does not prove the absence of contrary results.However, the available evidence shows that the significance of the signals released by macrophages and monocytes is highly context-dependent. In the study on human monocytes, the simultaneous activation of different Toll-like receptors reduced the secretion of certain chemokines, CCL1 and CCL2, without reducing CCL4 [2]. This does not contradict the communicative role of macrophages, but indicates that they do not always increase all recruitment signals: they can also selectively modify their composition and, consequently, the type of cells involved in the response.

8. QUADRO COMPARATIVO E SINTESI DELLE EVIDENZE

The table distinguishes the publication subject to the Evidence Review from the independent studies used to verify the specific passage of the book chapter.

Quadro comparativo

Reference	Study type	Population or model	Main result	Direction of evidence	Strength of evidence
Original study	Narrative review	Literature on alternative macrophage activation	Describes the role of IL-4 and IL-13 in modifying macrophage biology and their immune functions.	biologically consistent evidence	moderate
[1]	Animal	Mice with lipopolysaccharide-induced peritoneal inflammation	Macrophages produce CXCL1/CXCL2 and their reduction limits neutrophil recruitment to the peritoneum.	direct confirmation	moderate
[2]	Cellular	Human monocytes and cells differentiating into macrophages	Stimulation modifies chemokine secretion and the chemotactic activity of the conditioned medium on mononuclear cells.	direct confirmation	moderate
[3]	Cellular	Human monocyte-derived macrophages and U937 cell line	Paracrine communication between macrophages modulates the secretion of TNF-alpha, IL-6, and IL-10.	indirect confirmation	moderate

9. SINTESI EDITORIALE E CONCLUSIONI

CONCLUSIONS

The analyzed publication consistently supports the idea that macrophages are regulatory cells capable of adapting their functions to the immune signals they receive. The passage in the book regarding cytokine release and response modulation is confirmed by independent experimental studies. The link to the recruitment of other cells is particularly well-supported in animal and cellular models, but requires further validation in humans and across different pathological contexts.

Aggiornato al 24/11/2026. Questo contenuto riflette una sintesi divulgativa delle evidenze scientifiche al momento della pubblicazione e non sostituisce il parere medico.

10. TRANSPARENCY AND SCIENTIFIC RESPONSIBILITY

Artificial Intelligence was used solely as a tool for editorial and documentary support. All content, interpretations, bibliographic citations and conclusions have been verified, reviewed and approved by the author, who assumes full scientific responsibility for them.

The manuscript was also subjected to independent peer review prior to publication.
To ensure the greatest transparency, the complete history of the article, including the dates of submission, revision, acceptance and publication, as well as information on the peer review process, is available on the dedicated Article History page.

11. RIFERIMENTI BIBLIOGRAFICI

[1] **Mast cell and macrophage chemokines CXCL1/CXCL2 control the early stage of neutrophil recruitment during tissue inflammation**
De Filippo et al., 2013
Blood
DOI: https://doi.org/10.1182/blood-2013-02-486217

[2] **Toll-like receptor cross-talk in human monocytes regulates CC-chemokine production, antigen uptake and immune cell recruitment**
Sabbatucci et al., 2011
Immunobiology
DOI: https://doi.org/10.1016/j.imbio.2011.04.005

[3] **Analysis of single-cell cytokine secretion reveals a role for paracrine signaling in coordinating macrophage responses to TLR4 stimulation**
Xue et al., 2015
Science Signaling
DOI: https://doi.org/10.1126/scisignal.aaa2155