Hepatology Snapshot:

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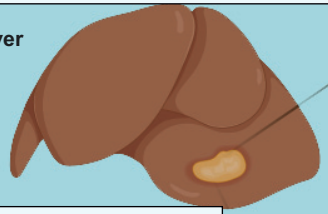
The underlying cellular immune pathology of *Entamoeba histolytica*-induced hepatic amoebiasis

Julie Sellau[1]*, Marie Groneberg[1], Stefan Hoenow[1], Hannelore Lotter[1]*

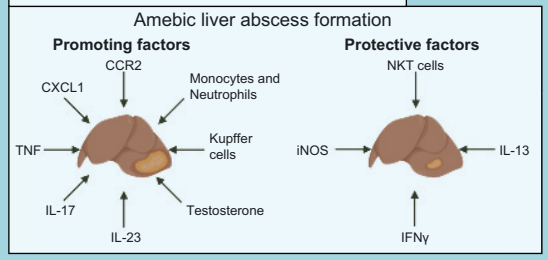
[1]Department of Molecular Biology and Immunology, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany
*Corresponding Authors. Address: Department of Molecular Biology and Immunology, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany; Tel.: (+49) 42818-475 or -443; fax: (+49) 42818-512
E-mail adresses: sellau@bnitm.de (*J. Sellau*) lotter@bnitm.de (*H. Lotter*) Twitter: @LotterLab

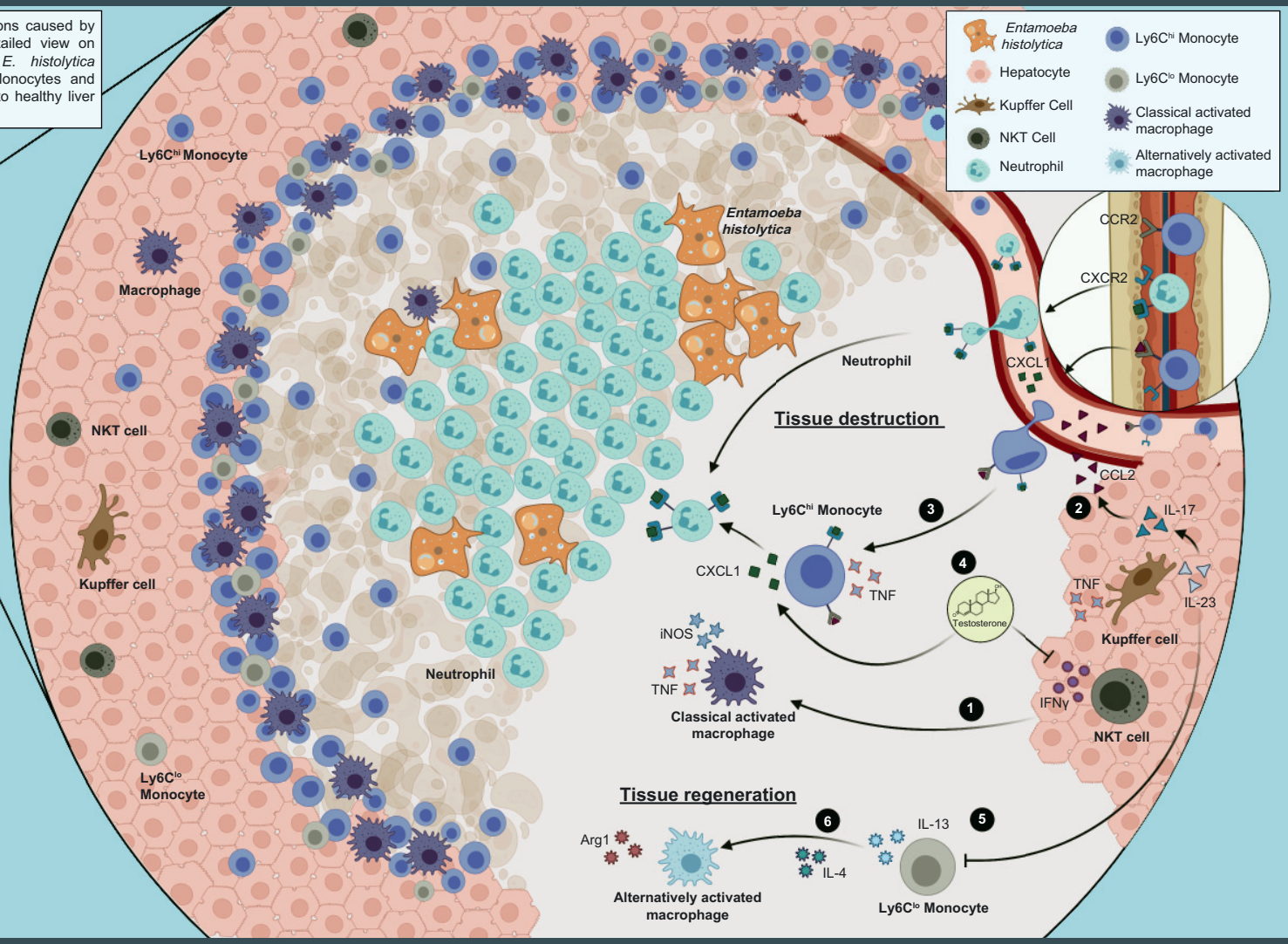
Characteristic histological organization resulting from the immune reactions caused by *Entamoeba* (E.) *histolyica*-induced liver abscess formation, with a detailed view on immune-cell-mediated tissue destruction and regeneration. Here, *E. histolytica* trophozoites are surrounded by neutrophils and lysed liver tissue. Monocytes and macrophages are mainly localized at the edge of the abscess adjacent to healthy liver tissue.

Murine liver



Immune cells and the destroyed liver tissue form a cytokine environment, which in turn leads to further tissue destruction. At an early stage of infection, NKT cells release IFNγ, which activates the TNF- and iNOS-secreting macrophages responsible for better parasite killing ❶. The CCL2 expression is promoted by the early presence of IL-23 and IL-17 ❷. CCL2 is responsible for the recruitment of CCR2-expressing Ly6C^{hi} monocytes from the bone marrow through the blood stream to the site of infection, where these cells express the potent neutrophil recruiting factor CXCL1❸. Testosterone further promotes immune pathology by inhibiting the IFNγ release by NKT cells and increasing the CXCL1 production of Ly6C^{hi} monocytes❹. Tissue regeneration is mediated by IL-13 from Ly6C^{lo} monocytes. In combination with IL-4, IL-13 leads to the generation of alternatively activated macrophages, which release Arginase 1 and promote tissue regeneration❻. This mechanism can be inhibited by IL-23❺.





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Background

Intestinal infection with the protozoan *Entamoeba (E.) histolytica* occurs by oral ingestion of cysts via contaminated food or water and usually remains asymptomatic. However, the parasite can break through the gut wall and accidentally enter the bloodstream via unknown mechanisms. From the bloodstream, *E. histolytica* can reach various organs and cause abscesses, particularly in the liver. A possible cause of initial tissue destruction may be certain pathogenicity factors such as lectins, amoebapores and peptidases of the parasite, which in turn lead to abscess formation.[1] If untreated, the amoebic liver abscess (ALA) can lead to death in humans. To cure this invasive infection, metronidazol is administered together with paromomycin to eliminate trophozoites from the infected tissues and the gut.[2]

Immunopathology

Nevertheless, the development of ALA cannot only be explained by the invasion of *E. histolytica* trophozoites alone, but rather primarily by an unbalanced innate immune response of the host. The manifestation of ALA is characterized by a capsule formation of immune cells around *E. histolytica* trophozoites. This cellular organization is defined by monocytes and macrophages, which are mainly located adjacent to the lysed tissue at the edge of the abscess. In the center *E. histolytica* trophozoites can be found surrounded by neutrophils.[3] Due to the initial tissue damage caused by invading parasites, resident cells of the liver, *e.g.* Kupffer cells, start to release cytokines such as CCL2 and TNF. The concentration of CCL2 is further increased by the initiation of the IL-23/IL-17 immune axis,[4] with IL-17 involved in the recruitment and modulation of neutrophils.[5] CCL2 leads to the recruitment of CCR2-expressing Ly6C^{hi} monocytes from the bone marrow to the site of infection. These monocytes in turn express TNF, which triggers the expression of CXCL1 in an autocrine manner.[6] CXCR2-expressing monocytes as well as neutrophils are attracted by CXCL1, which enhances ALA-specific immunopathology.

A special characteristic of hepatic amebiasis is the different manifestation of the disease in men and women. Although women have a higher parasite burden, men are more susceptible to the development of ALA, with an increasing risk at puberty.[7] In the mouse model, which reflects the same sex difference as in humans, testosterone was identified to enhance abscess development.[8] The presence of testosterone leads to a decreased expression of IFNg by NKT cells, a potent macrophage-activating cytokine. The identification of an NKT cell ligand in the membrane of *E. histolytica* trophozoites induces the release of IFNg, confirming the assumption that these cells are crucial for abscess formation.[8] Indeed, the absence of NKT cells in Jα18 knock-out mice led to an increased risk of ALA formation.[9] In addition, NKT cells are more abundant in women than in men, further increasing the protection against the development of a hepatic abscess.[10]

Moreover, testosterone enhances the expression of CXCL1 by Ly6C^{hi} monocytes, which promotes the destructive immune pathology of ALA. In fact, this observation has been confirmed with *E. histolytica* antigen-stimulated human monocytes, showing a direct effect of testosterone on monocytes.[6]

Regeneration

However, unlike in humans, mice are able to recover from abscesses. Ly6C^{lo} monocytes contribute to a major extent to the regeneration of liver tissue. The early release of IL-13 by Ly6C^{lo} monocytes during abscess development is key to regeneration, but can be inhibited by IL-23. Together with the increased release of IL-4 during hepatic amebiasis, IL-13 polarizes Ly6C^{lo} monocytes into alternatively activated macrophages, which are potent producers of arginase 1. This enzyme competes with iNOS for L-arginine and thus inhibits further proinflammatory processes, leading to immune suppression and recovery.[11]

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Conflict of interest

The authors declare no conflict of interest.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Both the design and the concept were created by all authors. All authors read and approved the manuscript.

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Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.03.018.

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Authors names in bold designate shared co-first authorship

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