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The whole process of macrophage–*Treponema pallidum* interactions: Opsonic phagocytosis, nonopsonic phagocytosis and active invasion

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ABSTRACT

Despite the acknowledged central role of opsonophagocytosis in the process of syphilis, the interaction between *Treponema pallidum* and human macrophages during nonopsonophagocytosis and active invasion remains controversial. To investigate whether nonopsonic phagocytosis and active invasion, similar to opsonic phagocytosis, also participate in the process of macrophage–*T. pallidum* interactions, monocyte-derived macrophages were used to study the interactions of *T. pallidum* and macrophages in the presence of nonsyphytic or syphilitic serum and in the absence of serum *in vitro* using indirect immunofluorescence and flow cytometry to quantitate treponeme–macrophage interactions. The results showed that macrophages phagocytose *T. pallidum* under both nonopsonizing conditions (no serum or normal human serum (NHS)) and in the presence of opsonizing serum (secondary syphilitic serum (SSS)) in a time-dependent manner. The percentages of spirochete-positive macrophages in the SSS group were higher than those in the NHS and no-serum groups. Blocking $Fc_{\gamma}R$ or inactivating complement caused a significant decrease in the percentage of spirochete-positive macrophages in the SSS group but did not cause a decrease in the percentages of spirochete-positive macrophages in the NHS and no-serum groups. In addition, after inhibiting macrophage phagocytosis, approximately 30% of macrophages internalized spirochetes, verifying that *T. pallidum* actively penetrated macrophages rather than was ingested by them. This study provides evidence that opsonic phagocytosis, nonopsonic phagocytosis and active invasion are all active during *T. pallidum*–macrophage interactions and reveals a process of treponeme–macrophage interactions in *T. pallidum* pathogenesis.

1. Introduction

Syphilis, which is caused by *Treponema pallidum*, is an infectious sexually transmitted disease that is distributed worldwide[1]. Syphilis affects nearly 36 million people globally and continues to be a major public health threat [2,3]. The pathogenesis of syphilis can be considered a battle between the invasive ability of *T. pallidum* and the proficiency of the host's immune responses at finding and destroying spirochetes. Macrophages are a critical component of the host innate immune response and are on the first line of defence against invading *T. pallidum*[4], resulting in the release of cytokines and chemokines, as well as the phagocytosis of *T. pallidum*[5,6]. Lukehart et al. verified that opsonic antibodies enhance rabbit macrophage phagocytosis [7,8]. Similar to the rabbit experiment results, it has also been found that human syphilitic serum enhanced macrophage uptake of spirochetes [9]. Despite the acknowledged central role of opsonophagocytosis during syphilis[10–12], the interactions between *T. pallidum* and human macrophages during the period when antibodies have not yet been produced (nonopsonic) or at sites that opsonins are absent, such as the lung, remain controversial. Kelly L. et al. found that *T. pallidum* binds only to macrophages with nonsyphilitic serum or without serum without causing a concomitant increase in spirochete uptake[12]. However, light and electron microscopy examinations of syphilis specimens confirmed that macrophages infiltrated the initial site of infection early, which suggests that *T. pallidum* may be ingested independently of the presence of opsonins. In addition, Azar. et al. initially described treponemes within plasma cells isolated from a human chancre[13]. Sykes et al. detected treponemes within epithelial cells, white blood cells,

Abbreviations: NHS, normal human serum; SSS, secondary syphilitic serum.

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