Tuberculosis 94 (2014) 8–14

Contents lists available at ScienceDirect

Tuberculosis

journal homepage: http://intl.elsevierhealth.com/journals/tube

COMMENT

A new unifying theory of the pathogenesis of tuberculosis

Ian M. Orme*

Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, CO 80523, USA

ARTICLE INFO

Article history:
Received 12 March 2013
Received in revised form
24 July 2013
Accepted 29 July 2013

Keywords:
Tuberculosis
Latency
Persistence
Reactivation

SUMMARY

It is set in stone that *Mycobacterium tuberculosis* is a facultative intracellular bacterial parasite. This axiom drives our knowledge of the host response, the way we design vaccines against the organism by generating protective T cells, and to a lesser extent, the way we try to target anti-microbial drugs. The purpose of this article is to commit total heresy. I believe that *M. tuberculosis* can equally well be regarded as an extracellular pathogen and may in fact spend a large percentage of its human lung "life-cycle" in this environment. It is of course intracellular as well, but this may well be little more than a brief interlude after infection of a new host during which the bacterium must replicate to increase its chances of transmission and physiologically adapt prior to moving back to an extracellular phase. As a result, by focusing almost completely on just the intracellular phase, we may be making serious strategic errors in the way we try to intervene in this pathogenic process. It is my opinion that when a TB bacillus enters the lungs and starts to reside inside an alveolar macrophage, its central driving force is to switch on a process leading to lung necrosis, since it is only by this process that the local lung tissue can be destroyed and the bacillus can be exhaled and transmitted. I present here a new model of the pathogenesis of the disease that attempts to unify the pathogenic process of infection, disease, persistence [rather than latency], and reactivation.

1. A new model of pathology and pathogenesis

The process of infection is initiated when the bacterium [or perhaps even a cluster or clump, see below], delivered in a water droplet into an alveolus in the lung, is ingested by an alveolar macrophage. Classical electron microscopy studies suggests that at least some of these cells adhere to the alveolar epithelial surface and substantially extend and spread out their cell membranes [Figure 1A]. This is followed by a process which is critical to the bacterium because it must not only survive, but find its way into the interstitium of the lung if it is going to establish an infection. This process is still poorly understood, but it could involve or include the ESX secretion systems now being increasingly well characterized, although to date this has not been specifically shown [1–3]. Once in the interstitium the bacillus [or bacilli, if there is some initial replication in the alveolar macrophage or if the ingested droplet contains a clump of bacteria] can now be taken up by monocytes leaving the local capillary bed, or by dendritic cells [which roam the lung parenchyma in large numbers] arriving from the airspace surface or from lymphatic capillaries [Figure 1B]. Indeed, there is now convincing evidence that very early carriage of bacilli out of the initial sites of implantation and into the draining lymphatics is a key event in triggering the acquired immune response [4–6].

There is a massive amount of information regarding survival mechanisms employed by the bacillus inside macrophages, which will not be recounted here. The general concept is that there is a counter-balance between the macrophage attempting to kill the bacillus, and the bacillus taking counter-measures. Most of these mechanisms have been observed in vitro, but whether these all occur in the lungs is very much less clear. One example is host cell apoptosis; this is readily observed in cell cultures, but macrophages infected with virulent strains rapidly become necrotic not apoptotic [7], as do neutrophils [8], and for that matter apoptotic cells in the lungs of infected animals that can be seen under the microscope in vivo are relatively rare [7,9].

The next stage is equally critical, because now the bacterium needs to replicate and drive the initial infection into an active disease state. Here, one can argue that the organism has evolved to drive a single event. It is not, as a recent review [10] tries to argue, to come to some sort of balance with the host response. Instead, the bacillus drives the mechanism essential to its transmission – *necrosis*. A bacillus in a macrophage in a granuloma cannot infect the next victim; only an extracellular bacillus in a necrotic cavity can achieve this. In hindsight, one can argue that our concepts of

* Tel.: +1 970 491 5777.
E-mail address: ian.orme@colostate.edu.

1472-9792/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tube.2013.07.004

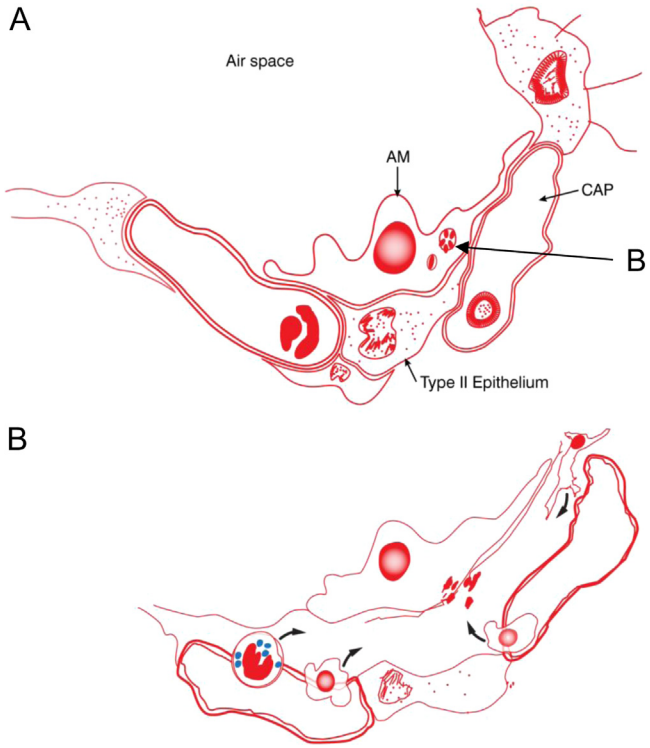

Figure 1. [A] In the first stage of the infection process an alveolar macrophage engulfs a bacterium ["B", or possibly a clump/cluster, see text]. The cell then extends its cytoplasm and spreads across the alveolar epithelial surface. Soon afterward [perhaps involving the use of their ESX system peptides?] the bacilli somehow cross the basal membrane [panel B]. This creates local inflammation and swelling between the alveolar epithelium and the capillary endothelium allowing the influx of tissue fluid. This in turn allows the influx of macrophages and neutrophils from the blood, and dendritic cells from the lung parenchyma.

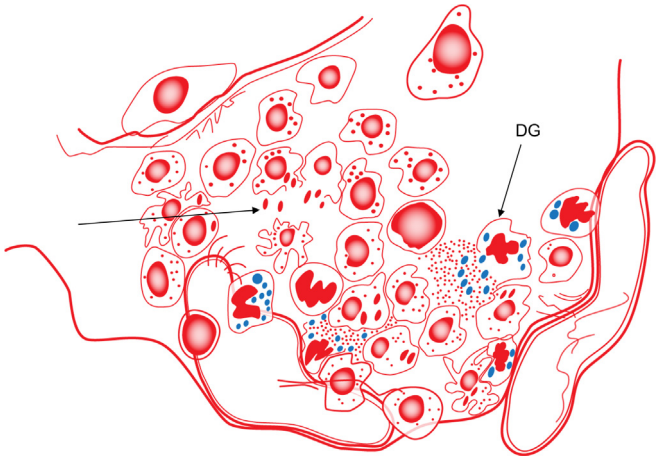

Figure 2. Initial infection now triggers a considerable influx of cells which creates an initial lesion or infectious focus. In most cases the incoming macrophages kill the bacteria but when this fails the bacteria multiply and these macrophages are themselves killed, releasing bacteria [arrow]. Released bacilli are probably at this stage phagocytosed by newly arriving cells, amplifying the process. At this point the influx is predominantly macrophages, with some neutrophils and a smaller number of lymphocytes. The neutrophils produce and secrete oxygen radicals and while this probably has little impact on the mycobacteria these radicals cause oxidative damage to the capillary endothelium, and in addition these structures [and probably adjacent lymphatic capillaries as well] are compressed and collapsed by the continuing cellular influx. These events, probably coupled with local neutrophil death and degranulation [DG], create tiny foci of initial necrosis [visible in the lungs of guinea pigs by 5–7 days].

bacterial survival followed by chronic disease and a state of dormancy or latency have primarily arisen from our studies in mice – an animal species in which the bacillus has difficulty in driving any degree of necrosis at all [11].

In most models to date the generation of necrosis is regarded as an endpoint; in the popular Lurie/Dannenberg model T cell-mediated "excessive DTH" drives necrosis and the subsequent florid replication of bacilli in cavities – despite the fact that DTH T cells could never survive in necrosis, nor can florid bacterial replication even be seen. In fact, in complete contrast, I would argue that the process of necrosis is the *starting point* rather than the endpoint. In studies in my laboratory, local foci of tissue damage occur very rapidly – in the guinea pig model these are evident in 5–10 days, and we think they coalesce to form the central necrosis characteristic of both guinea pigs and humans [9,11]. Such damage creates inflammation and this attracts neutrophils, a cell we feel is a key player in the overall process yet mostly ignored to date [an attitude now hopefully changing] [12,13].

Under the microscope evidence of interstitial inflammation becomes evident as the infectious focus becomes established [Figure 2]. Because the interstitium becomes inflamed and swells with tissue fluid, this allows macrophages and neutrophils to begin to accumulate. Some neutrophils may be able to kill bacilli [14] at this point, but these cells are short lived and some will almost certainly degranulate, releasing enzymes that may damage the basement membrane and the vascular endothelium; this, we suspect, is the very beginning of the necrosis that is the hallmark of the disease. Unfortunately, moreover, one of the primary anti-microbial mechanisms of neutrophils is the production of toxic oxygen radicals. The cell wall of the bacillus is adept at scavenging these radicals [15], but the local capillary endothelium is not, and as a result the local microvasculature rapidly undergoes severe oxidative damage [16], as well as compression by the developing granuloma. These processes, I would propose, sets in motion a necrotic process which is irreversible, at least in the sense that host mechanisms, such as wound healing and the onset of dystrophic calcification, cannot fully prevent it. As the local capillary bed collapses as a result of this cumulative damage, the ability of T cells and macrophages to infiltrate the central areas of the lesion becomes increasingly compromised. The tissue fluid can still deliver oxygen to some extent, but the outcome is a region becoming increasingly hypoxic [17,18]. The surviving bacilli must adapt to this, but [I would propose] not to nutrient starvation. While the latter is a popular idea [especially in models to screen drugs for "latent" disease], the reality is that the lesion probably contains a simply vast amount of host cell membranes and cholesterol left behind by dying [short lived] neutrophils. This may be a key event in ensuring the persistence of bacilli within necrosis, and indeed could provide a 2-carbon source that could sustain these bacilli for many years [19].

Such mechanisms also threaten the bacillus itself, and so it quickly adapts into a stress response, primarily controlled by the DosR regulon, a process that has been very well characterized [20–22]. This is generally interpreted as a response to full blown host immunity in which the surviving bacteria switch on a large number of stress-related or "latency" genes that enables them to "hide" in a state of latency or dormancy from which they may be able to safely reappear at a later time. But are we completely misinterpreting this information? In my alternative model, the bacilli are sensing these events and adapting accordingly. True, some bacteria will be killed off, but the generation of the host response indicates necrosis will soon be emerging, and with it cavitation, escape, and transmission. The survivors will not have it easy, at least for a while, so DosR and other genes need to be turned on. In other words, the DosR response is not one of preparing for latency and "switching off", it is *quite the reverse* – it is a "switching on and adapting" response