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REVIEW

HIV-1 and the *Mycobacterium tuberculosis* granuloma: A systematic review and meta-analysis

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SUMMARY

Infection with HIV-1 greatly increases the risk of active tuberculosis (TB). Although hypotheses suggest HIV-1 disrupts *Mycobacterium tuberculosis* (Mtb) granuloma function, few studies have examined this directly. The objective of this study was to determine what evidence exists about the effect HIV-1 co-infection has upon Mtb granulomas. A systematic search of PubMed, Web of Science, and Medline up to 20 March 2015 was conducted, to identify studies comparing Mtb-infected tissue from HIV-1 infected and uninfected persons, or HIV-1 infected persons with stratified peripheral CD4 T cell (pCD4) counts. We summarized findings that focused on how HIV-1 changes granuloma formation, bacterial presence, cellular composition, and cytokine production. Nineteen studies with a combined sample size of 899 persons were included. Although studies frequently were limited by variable or inadequately described definitions of outcomes and analytical methods, HIV-1 was found to be associated with increased bacillary load within Mtb-infected tissue. Reductions in pCD4 counts within co-infected persons associated with both poorer granuloma formation and higher bacterial load. The high degree of heterogeneity among studies combined with experimental limitations made it difficult to conclusively support previously published and prevalent hypotheses about HIV-1/Mtb co-infection granulomas. To elucidate the validity of these hypotheses we have described areas that can be improved in future studies in order to clarify the influence HIV-1 co-infection has upon the Mtb granuloma.

1. Introduction

Tuberculosis (TB) and HIV-1 are two of the leading infectious causes of death worldwide and TB is the leading cause of death among HIV-1 infected persons [1]. Once infected with *Mycobacterium tuberculosis* (Mtb), HIV-1 infected persons have increased morbidity and mortality due to TB compared to HIV-1 uninfected persons [2]. As peripheral CD4 T cell (pCD4) counts fall, susceptibility to active and disseminated TB increase, however, HIV-1 infected persons with relatively preserved pCD4 counts are also at increased risk [3]. It has been hypothesized that the primary cause for increased TB susceptibility in HIV-1 infected persons is due to immunological disruptions of the Mtb granuloma [4,5].

The granuloma is the hallmark of TB. Granulomas consist of a collection of organized immunological cells that form in response to Mtb infection [6]. Granulomas commonly consist of infected and recruited macrophages, differentiated epithelioid cells, all surrounded by a lymphocyte layer. The relationship between the granuloma and TB is complex and not fully understood because granulomas can prevent dissemination and kill Mtb, but also allow persistence of Mtb and even be permissive to its growth [7,8]. This illustrates the delicate balance between bacterial growth and death within the microenvironment of the granuloma and that granulomas form an incompletely effective or even bacterium-permissive immunological response [7,9]. It is hypothesized that HIV-1 disrupts this balance by causing granulomas to be more disorganized, killing resident CD4 T cells, and dysregulating normal T cell, and macrophage function (Table 1) [4,5,10–14], leading to an

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Table 1
Hypotheses how HIV-1 manipulates Mtb granulomas.

Review (first author, year published)	Main hypotheses regarding granulomas in HIV-1/Mtb co-infected persons
Ledru, 1999 [10]	HIV-1's ability to manipulate cytokine and nitric oxide production that are recruited to the granuloma may play an important role in increasing bacterial dissemination.
Bocchino, 2000 [11]	Poor granuloma formation within co-infected persons most likely results from a disruption in the pro- and anti-inflammatory production of cytokines and an increase in cell death of CD4 T cells.
Lawn, 2002 [5]	Granulomas within co-infected persons will be poorly formed and contain increased bacterial growth through the impairment of cellular recruitment and cell-mediated granulomatous response.
Diedrich, 2011 [4]	Granulomas within co-infected persons will have impaired architecture, reduced CD4 T cell counts, impaired T cell and macrophage function, and increased cell death.
Kwan, 2011 [12]	HIV-1 replication may be induced by Mtb-infected macrophages that will indeed lead to HIV-1 infection of adjacent macrophages and CD4 T cells and activated CD4 T cells will increase HIV-1 replication
Geldmacher, 2012 [13]	Preferential depletion of Mtb-specific and total CD4 T cells may play a significant role in granuloma disruption within HIV-1 infected persons
Ansari, 2013 [14]	HIV-1 enters granulomas and causes CD4 T cell apoptosis, depletion, and disrupted recruitment of T cells, which leads to granuloma disorganization.

increase in susceptibility to both active and disseminated TB disease.

Many studies in humans that support these hypotheses have measured immunological responses within non-tissue resident cells: peripheral blood mononuclear cells (PBMC), bronchoalveolar fluid (BALF), and pericardial fluid (PCF) [15–18]. These studies have demonstrated impaired Mtb-specific T cell activity [15,16,18] and killing of Mtb-specific peripheral CD4 T cells [19], and total BAL CD4 T cells [17] in persons infected with HIV-1. Although these data are convincing, there are significant variations in cellular composition and Mtb-specific immunological responses within PBMC, BALF, PCF, and granulomas [20,21]. Extrapolating data from non-tissue resident cells to what is occurring within granulomas may not be appropriate [22]. This illuminates a need to study human granulomas directly in HIV-1/Mtb co-infected persons to better understand how HIV-1 manipulates the TB granuloma. Understanding how HIV-1 manipulates granulomas directly will elucidate the mechanistic cause HIV-1 exploits that increases TB susceptibility.

We systematically reviewed HIV-1/Mtb co-infection literature that examined Mtb granulomas directly. The objective of this systematic review and meta-analysis was to elucidate how Mtb-infected tissues differ between HIV-1 infected and uninfected persons. We focused on studies that reported how HIV-1 changed: granuloma formation [23–29], granuloma organization [23,26–28,30–35], granuloma caseation [23,25,26,29–33], Mtb growth [23–25,27,31,32,35,36], cellular populations [23,26,30–33], cytokine expression [30,31,37] and HIV-1 virion presence within excised tissue [33,38]. To help reduce some of the variability observed within this literature our second objective of this review was to illuminate future strategies to study, analyze, and report granuloma-based data.

2. Methods

2.1. Search strategy and selection criteria

PubMed, Web of Science, and Medline were searched using predetermined combinations of terms (Supplemental Table 1) for relevant peer reviewed studies (through 20 March 2015) that reported histological data in TB diseased tissue from HIV-1/Mtb co-infected persons. We reviewed original articles published in all languages. In addition to the database search, we screened citations in the full-text articles reviewed here, published reviews, book chapters, and suggested papers from experts in the field.

The primary objective of this review was to identify how Mtb granulomas from HIV-1/Mtb co-infected persons differed from granulomas obtained from HIV-1 uninfected persons. Studies were eligible for inclusion if they compared the histology of Mtb infected tissue from HIV-1 infected and uninfected persons, or from HIV-1 infected persons with stratified pCD4 counts. Studies were required to include an acceptable means of defining HIV-1-infected and uninfected groups (either HIV-1 serology or a documented past history of HIV-1 infection, or for studies prior to 1990, an acceptable HIV/AIDS diagnosis by World Health Organization criteria at the time of publication) and confirming TB diagnosis (microbiology or histology consistent with TB, with or without a consistent clinical picture including course of illness and response to treatment). Studies were excluded if the method of biopsy was only fine-needle aspiration (FNA) as this method of excision was unlikely to preserve granuloma architecture and may not capture entire granulomas within the target tissue. Where studies reported or appeared to report on the same or overlapping persons, the results from the earlier study were excluded. Reviewers independently assessed the eligible articles for inclusion and exclusion criteria; disagreements were resolved by consensus. The included studies were assessed for quality of study design and potential limitations to findings.

2.2. Data extraction

Results from the individual studies were categorized into the following outcomes for comparison between HIV-1/Mtb co-infected and HIV-1 uninfected persons, or HIV-1-infected with stratified pCD4 counts: 1) proportion of biopsied samples with granulomas present, 2) quality of granuloma formation (quality of granuloma formation was defined independently within each study), 3) cellular and cytokine presence, 4) proportion of biopsied samples containing Mtb (acid fast bacilli [AFB] or culture positivity [CFU], 5) bacillary load within AFB+ samples, and 6) HIV-1 virion presence.

2.3. Statistical analysis

For outcomes where studies reported individual quantitative or semi-quantitative results for the different outcomes HIV-1/Mtb co-infected and Mtb-only infected persons, a meta-analysis was performed using the Cochrane Database's RevMan program. We calculated summative risk ratios for changes in 1) granuloma presence, 2) quality of granuloma formation, 3) AFB presence 4) CFU in HIV-1/Mtb-co-infected versus Mtb-only infected persons and 5) AFB load. Where results were categorically scored and not simply dichotomous (for quality of granuloma formation and AFB load), the proportions of persons in each group with the highest scores (for well-formed granulomas and AFB load) or lowest scores (for poorly formed granulomas) were used in meta-analyses. Data sets were treated as dichotomous and risk ratio with 95% CIs were

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