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Do B-1 cells play a role in response to *Mycobacterium tuberculosis* Beijing lineages?

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ABSTRACT

We highlight the need to include an analysis of the B-1 B cell subset to complement the characterization of the cell-mediated immune response to the *Mycobacterium tuberculosis* Beijing lineage. The literature describes the B-1 cell repertoire's involvement in the cell-mediated response within granulomas, which is different from the classic antibody response B cells are generally associated with. Specifically, the B-1 B cell subset migrates from other compartments along with other cells to the infection site. We provide details to complement the reported results from Cerezo-Cortes *et al*.

We read with great interest the article by Cerezo-Cortes *et al* [1]. The authors described the differences in pathogenesis between *M. tuberculosis* Classical-Beijing and Beijing-like SIT190 (BL) strains. Cell- and humoral-mediated immunity, as measured by animal survival, lung bacillary load, and histopathological damage, were described. Their approach was guided by differential mice lung gene expression profiles obtained during the early, intermediate, and, late disease phases following infection with these two pathogens. They observed more extensive pneumonia and rapid death after infection with the BL strain compared to the Classical-Beijing strain. We would like to highlight a few points to complement their findings.

We agree with the notion that this study corroborates previous findings that Modern Beijing lineage strains show higher virulence than Ancestral Beijing lineage strains [2]. Modern Beijing strains have adapted to the human environment, resulting in increased prevalence and enhanced bacterial pathogenicity. *In vivo* models have shown extensive pneumonia and necrosis occupying up to 80% of the lungs as a result of exposure to the Modern Beijing strain [2]. The *M. tuberculosis* BL infection revealed an over-expression of anti-inflammatory milieu cytokines and chemokines mRNA of several genes. This led to suppression of the immune response which in turn allowed high bacterial replication followed by an intense inflammatory response. Taking all into consideration, Cerezo-Cortes provides strong evidence of a differential response at the lung level according to bacterial genetics.

Mycobacteria drug resistance is often associated with decreased ability to replicate and survive during infection. The survival, reproduction, and transmission of multi drug resistant and extremely drug resistant (MDR/XDR) *M. tuberculosis* strains have a high metabolism cost leading to lower transmission and virulence [3,4]. Surprisingly, this phenomenon does not seem to affect the BL XDR strain's virulence capacity; in fact, the virulence of this strain was slightly higher than that of the MDR Classical-Beijing strain in the *in-vitro* experiments conducted by Cerezo-Cortes and colleagues. They report that BL strains replicate more efficiently and induce higher pro-inflammatory cytokine production *in vitro* during infection compared to the Classical-Beijing strain. A plausible explanation is that genetic alterations in the BL strain may have favored the selection of highly virulent bacteria. *In vivo* experiments have shown that extremely drug resistant *M. tuberculosis* strains (lineage 4) induce reduced lung pathology when compared to drug-sensitive or multidrug-resistant *M. tuberculosis* strains after infection [5]. In other words, an increased degree of drug resistance is associated with decreased murine virulence [5]. These observations support the *in vivo* findings observed by Cerezo-Cortes and colleagues.

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B cells play an important role during *M. tuberculosis* infection and host interaction due to their anti-inflammatory and antibody responses [6,7]. They contribute to local immunity, optimizing the acute inflammatory reaction and perpetuating the chronic containment of the disease [8,9]. Specifically, there is evidence of granuloma infiltration by B cells in mice lungs infected with *M. tuberculosis*. In studies of chronic tuberculosis in *M tuberculosis*-infected mice, granuloma display characteristics of lymphoid structures, with follicular aggregation of B cells as well as expression of the homeostatic chemokines CXCL13 and CCL19 [10]. Similar participation of B-cell lung granuloma after *M tuberculosis* infection has also been observed in non-human primates [11]. Phuah and colleagues described the B-cell and plasma-cell populations within granulomas of infected animals and reported the presence of B-cell clusters within the granuloma. These B-cell clusters included cells expressing Ki-67, CXCR5, and HLA-DR, suggesting an activation status. In the Phuah *et al.* study, the granulomas and thoracic lymph nodes showed plasma B cells secreting mycobacteria-specific IgG antibodies. Recently, Carow and colleagues depicted the 3-dimmensional appearance of lymphoid-rich areas within the granuloma and reported an over-representation of CD19 mRNA expressed by B cells during tuberculosis infection [12]. In fact, at the third week after *M. tuberculosis* infection, they noted a sparse and indiscriminate expression of CD19 mRNA. In contrast, at later time points, they observed a strong focal distribution in lymphoid-rich areas, which resembled inducible B-cell follicles within the C57BL/6 granuloma. Taken together, this evidence supports the key role of B cells in the lung immune response to *M. tuberculosis* infection. Cerezo-Cortes and colleagues reported differences in the expression of genes involved in cell migration, such as those encoding the pro-inflammatory chemokines CCL-3 and CCL-4, over the course of infection. It has been shown that the cross-linking of B cell receptors upregulates the expression of these chemokines [13], and that CCL-3 production by B cells can regulate the B cell response in lymph nodes [14]. Moreover, Cerezo-Cortes *et al.* reported over-expression of *Dleu2* in BL strain-infected mice; this gene is involved in B cell proliferation control. These results taken together support a potential role of B cells in the differential response to Classical-Beijing and BL strain infections. Variation of this B cell response among Ancestral and Modern Beijing lineages should be further addressed.

The B cell compartment contains two subsets, the B-1 and B-2 cell subsets, which differ in phenotype and tissue distribution [15]. B-1 cells are distinct in their developmental origins, and many reside in the pleural and peritoneal compartments. B-1 cells are separated into two subsets (B-1a and B-1b), and are largely responsible for "natural" IgM production and secretion of anti-phospholipids and other self-reactive IgM. B-1 cells also secrete antibodies in response to bacteria-associated antigens via T-cell-independent mechanisms, including activation of B cell and Toll-like receptors [16,17]. B-1 cell activation is regulated by autocrine secretion of interleukin (IL)-10, while B-1 cell is induced by IL-12, IL-5 and interferon gamma, as well as pathogen-associated molecules, such as phospholipids [18]. All above evidence suggest B-1 cells are present during infection and disease.

In fact, B-1 cell subsets can be augmented during infection to alter the immune response against *Mycobacterium*. For example, Taylor and colleagues observed severe granulomatous pneumonia and tissue damage in the lungs of C57BL/6 mice previously infected with *M. tuberculosis* who were later therapeutically vaccinated with *M. leprae*-derived hsp65 DNA (Taylor *et al.*, 2005). When they looked at *ex-vivo* analysis from these lung cells, a high anti-inflammatory response, partially facilitated by B-1 cells, was observed. Later, a study by Russo and colleagues suggested that B-1 cells are able to migrate from the peritoneal cavity to the lungs as part of the protective response in mice chronically infected with *M. bovis* Bacillus Calmette-Guérin (BCG) (Russo and Mariano, 2010). They demonstrated that B-1 cells are present in the BCG-induced pulmonary lesions and were able to modulate the histological pattern of inflammation by altering the cellular response within the infected lung. Our research team recently demonstrated that exposure of *M. tuberculosis* H37Rv total lipids to both CD5$^+$ B-1a and CD5$^-$ B-1b cell subsets induced the secretion of total IgM and nonspecific anti-phospholipid IgM antibodies [19]. When following disease progression in mice with pleural *M. bovis* BCG infection, we noted that anti-cardiolipin IgM antibody levels decreased with bacterial clearance [20]. In light of Cerezo-Cortes *et al.*'s findings, we could hypothesize that the differences in IL-10 expression observed between BL strain-infected and Classical-Beijing strain-infected mice could be partially associated with the presence of B-1 cells in infected sites. The ability of Ancestral and Modern Beijing lineages to modulate the B-1 B cell subset response during acute and chronic infection has yet to be determined [1].

In summary, Cerezo-Cortes *et al.* contributes to our understanding of the cellular and humoral immune

response against *M. tuberculosis* BL and the Classical Beijing lineage in the lungs. We believe that the evolutionary acquisition of antibiotic resistance induced the observed variation in virulence. Also, future studies are warranted to further characterize the immune response among B cells and B-1 B cell subsets to Ancient and Modern Beijing strains in order to decipher the entire immunity picture. Such conclusions could advance vaccine development efforts, especially in regions where *M. tuberculosis* Beijing lineages are prevalent.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

[1] Maria Irene CC, Juan German RC, Gamaliel LL, et al. Profiling the immune response to Mycobacterium tuberculosis Beijing family infection: a perspective from the transcriptome. Virulence. 2021 Dec;12 (1):1689–1704. PubMed PMID: 34228582; PubMed Central PMCID: PMCPMC8265813.

[2] Ribeiro SC, Gomes LL, Amaral EP, et al. Mycobacterium tuberculosis strains of the modern sublineage of the Beijing family are more likely to display increased virulence than strains of the ancient sublineage. J Clin Microbiol. 2014 Jul;52 (7):2615–2624. PubMed PMID: 24829250; PubMed Central PMCID: PMCPMC4097719.

[3] Borrell S, Gagneux S. Infectiousness, reproductive fitness and evolution of drug-resistant Mycobacterium tuberculosis. Int J Tuberc Lung Dis. 2009 Dec;13 (12):1456–1466. PubMed PMID: 19919762.

[4] Bei J, Bigi MM, Lima A, et al. A phenotypic characterization of two isolates of a multidrug-resistant outbreak strain of mycobacterium tuberculosis with opposite epidemiological fitness. Biomed Res Int. 2020;2020:4741237. PubMed PMID: 32337252; PubMed Central PMCID: PMCPMC7168692.

[5] Smith KL, Saini D, Bardarov S, et al. Reduced virulence of an extensively drug-resistant outbreak strain of Mycobacterium tuberculosis in a murine model. PLoS One. 2014;9(4):e94953. PubMed PMID: 24733050; PubMed Central PMCID: PMCPMC3986381.

[6] Chan J, Mehta S, Bharrhan S, et al. The role of B cells and humoral immunity in Mycobacterium tuberculosis infection. Semin Immunol. 2014 Dec;26(6):588–600. PubMed PMID: 25458990; PubMed Central PMCID: PMCPMC4314354.

[7] Kozakiewicz L, Phuah J, Flynn J, et al. The role of B cells and humoral immunity in Mycobacterium tuberculosis infection. Adv Exp Med Biol. 2013;783:225–250.PubMed PMID: 23468112; PubMed Central PMCID: PMCPMC4184189.

[8] Maglione PJ, Xu J, Chan J. B cells moderate inflammatory progression and enhance bacterial containment upon pulmonary challenge with Mycobacterium tuberculosis. J Immunol. 2007 Jun 1;178 (11):7222–7234. PubMed PMID: 17513771.

[9] Ulrichs T, Kosmiadi GA, Trusov V, et al. Human tuberculous granulomas induce peripheral lymphoid follicle-like structures to orchestrate local host defence in the lung. J Pathol. 2004 Oct;204(2):217–228. PubMed PMID: 15376257.

[10] Kahnert A, Hopken UE, Stein M, et al. Mycobacterium tuberculosis triggers formation of lymphoid structure in murine lungs. J Infect Dis. 2007 Jan 1;195(1):46–54. PubMed PMID: 17152008.

[11] Phuah JY, Mattila JT, Lin PL, et al. Activated B cells in the granulomas of nonhuman primates infected with Mycobacterium tuberculosis. Am J Pathol. 2012 Aug;181(2):508–514. PubMed PMID: 22721647; PubMed Central PMCID: PMCPMC3409439.

[12] Carow B, Hauling T, Qian X, et al. Spatial and temporal localization of immune transcripts defines hallmarks and diversity in the tuberculosis granuloma. Nat Commun. 2019 Apr 23;10(1):1823. PubMed PMID: 31015452; PubMed Central PMCID: PMCPMC6479067.

[13] Krzysiek R, Lefevre EA, Zou W, et al. Antigen receptor engagement selectively induces macrophage inflammatory protein-1 alpha (MIP-1 alpha) and MIP-1 beta chemokine production in human B cells. J Immunol. 1999 Apr 15;162(8):4455–4463. PubMed PMID: 10201982.

[14] Benet ZL, Marthi M, Ke F, et al. CCL3 promotes germinal center B cells sampling by follicular regulatory T cells in murine lymph nodes. Front Immunol.

2018;9:2044.PubMed PMID: 30271404; PubMed Central PMCID: PMCPMC6146081.

[15] Baumgarth N. The shaping of a B cell pool maximally responsive to infections. Annu Rev Immunol. 2021 Apr 26;39:103–129. PubMed PMID: 33472004.

[16] Savage HP, Baumgarth N. Characteristics of natural antibody-secreting cells. Ann N Y Acad Sci. 2015 Dec;1362:132–142. PubMed PMID: 26104151; PubMed Central PMCID: PMCPMC4679694.

[17] Kreuk LS, Koch MA, Slayden LC, et al. B cell receptor and Toll-like receptor signaling coordinate to control distinct B-1 responses to both self and the microbiota. Elife. 2019 Aug 21;8. DOI:10.7554/eLife.47015. PubMed PMID: 31433298; PubMed Central PMCID: PMCPMC6703855.

[18] Smith FL. Baumgarth N. B-1 cell responses to infections. Curr Opin Immunol. 2019 Apr;57:23–31. PubMed PMID: 30685692; PubMed Central PMCID: PMCPMC6521837.

[19] Ordonez C, Savage HP, Tarajia M, et al. Both B-1a and B-1b cells exposed to Mycobacterium tuberculosis lipids differentiate into IgM antibody-secreting cells. Immunology. 2018 Feb 18. PubMed PMID: 29455451; PubMed Central PMCID: PMCPMC6050208. DOI:10.1111/imm.12909.

[20] Ordonez C, Tarajia M, Rivera R, et al. Total IgM and Anti-phosphatidylcholine IgM antibody secretion continue after clearance of mycobacterium bovis bacillus calmette-guerin pleural infection. Lung. 2017 Aug;195 (4):517–521. PubMed PMID: 28551717.