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Original Article

Eicosanoid and Cytokine Levels Differentiate between Stages of MTB Infection

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Abstract

Introduction: The need for biomarkers predicting the course of MTB infection and the necessity of specific therapy are well recognized. Recent data point to the role of cytokines and lipid mediators in protective immunity against tuberculosis.

Aim: We evaluated the balance between cytokines, and eikosanoids as a possible prognostic indicator in MTB infection.

Material and methods: The induced expression of effector and regulatory cytokines IFN-γ, TNF-α, IL-2, IL-17, IL-6, and IL-10 was measured in relation to the lipid mediators PGE2 and LXA4 in active TB infection (ATB, n=15) before and after therapy (ATB-T, n=6), established latent infection (LTBI, n=22), recent contacts of ATB (RC, n=12), and healthy controls (n=11) A flow cytometry microarray (CBA, BD Biosciences) and quantitative ELISA (SunRed Tech) were employed.

Results: The regulatory cytokines (RC) were characterized by a high potential for IL-17 and Th1 cytokine secretion, combined with low IL-6 expression, while ATB donors had a partially preserved TNF-α potential, and higher IL-6 expression. The PGE2-to-LXA4 ratio discriminated between situations with high bacterial load (ATB), and contained infection (LTBI, ATB-T), and defined clearly cut subgroups among RC and ATB donors.

Conclusions: Our results suggest that increased PGE2/LXA4 ratio coupled with high induced IL-10 level indicates infection after a recent contact. In the settings of ATB, increased ratio and low TNF-α level point to inefficient granuloma formation in the settings of ATB.

Keywords

eicosanoids, IL-17, MTB infection, PGE2/LXA4

INTRODUCTION

Although the overall burden of tuberculosis (TB) in the WHO European region is declining, TB remains a major health issue worldwide. TB is among the ten most deadly diseases in low income countries, with 1.5 million TB deaths in 2020 (up from 1.4 million in 2019).[1] TB incidence in Bulgaria is above the EU average with 1344 new diagnosis per year (19.2‰).[2] While a quarter of the world's population is infected with *M. tuberculosis* (MTB), only 10% of them will ever develop the disease. However, activation of latent TB infection (LTBI) is potentiated in the settings of immune deficiency with different origin.[3] Timely diagnosis and identification of cases with high risk of progression and activation are needed to limit TB spread, while avoiding heavy prophylaxis and treatment protocols, and selection of multi-resistant MTB strains.

Adaptive T-cell response is critical in MTB infection, with a leading role of Th1 effectors. Consequently, interferon gamma-release assays (IGRA) based on detection of memory MTB-specific T cells have gained wide diagnostic application.[4-6] Yet, it has become clear that they can neither predict the course of infection nor the need of specific therapy. Several studies have proposed that protective T cell response is associated with a multicytokine profile of effector cells (IL-2, IFN-γ, TNF-α) which activate macrophages for phagocytosis and bacteriolysis.[7,8]

The type of the immune response specific to MTB may actually depend on a wide range of factors associated with both innate and adaptive mechanisms. Recent data points out several effector and regulatory cytokines with possible role in the pathogenesis of MTB infection. A balanced immune inflammation is crucial for the induction of an adaptive immune response and efficient macrophage activation. IL-17 plays a key role in early neutrophil-mediated pulmonary inflammatory responses, T cell-mediated IFN-γ production and granuloma formation in the lung.[9,10] Accumulation of Treg in chronic infections limits inflammation-associated pathology but may also affect pathogen-specific response through soluble mediators (IL-10, TGF-β) or direct cell contact.[11]

Eicosanoids are a family of bioactive lipid mediators resulting from the metabolism of arachidonic acid that, similarly to cytokines, participate in inflammation and play a key role in shaping the adaptive response to MTB. Prostaglandins are the initial mediators of inflammatory response and stimulate recruitment of neutrophils and monocytes while lipoxins have anti-inflammatory activities and contribute to the resolution phase of the immune response.[12] The balance between pro- and anti-inflammatory eicosanoids may shape the course of infection.[13-15] Disease severity in TB has been associated with reduced ratio of prostaglandin E2 (PGE2)/lipoxin A4 (LXA4), rather than changes in the absolute levels of specific metabolites. A key counter-regulation between protective IL-1α, PGE2, and IL-17 signals against the pro-bacterial effects of IFNαβ/LXA4/IL-10 has been demonstrated in mice but awaits further study in men. It remains unclear whether eicosanoids can serve as biomarkers to distinguish activation of latent TB, to evaluate response to specific therapy or predict the outcome of a recent contact.[16-18]

AIM

In the present study, we evaluated the dynamics of cytokine secretion in association with the lipid mediators PGE2 and LXA4 at different stages of MTB infection: after a recent contact, in established latent phase, and in active untreated, and treated disease.

MATERIALS AND METHODS

Study populations

Whole peripheral blood samples were obtained from: A. Patients with latent TB infection that has been stable for at least 5 yrs, based on positive QuantiFERON®-TB In Tube assay (QFT >0.70 IU/ml), and absence of clinical symptoms (LTBI, n=22); B. Patients with active TB infection based on positive sputum smears for acid-fast bacilli, radiological findings, and/or MTB positive cultures, before (ATB, n=15) and after standard TB therapy following WHO guidelines (ATB-T, n=6); C. IGRA (-) recent contacts of ATB (RC, n=12). Exclusion criteria for all participants were HIV infection, diabetes, immunosuppressive diseases, and/or use of immunosuppressive medication. Bacillus Calmette-Guerin (BCG)-vaccinated, IGRA (-) healthy control individuals (HC, n=15) were also included in the study. Written informed consent was obtained from all participants. The protocol and informed consent were approved by the institutional review board of NCIPD (IRB 00006384, protocol N01/2018).

Quantitation of cytokines and lipid mediators

After centrifugation for 15 min at 1200 rpm the cell pellet was resuspended in complete RPMI/10% FCS for further stimulation. All samples were stimulated with phytohemagglutinin (PHA) (10 μg/ml) for 18 hours at 37°C, 5% CO_2 and the supernatants were collected.

The concentrations of lipoxin A4 (LXA4) and prostaglandin 2 (PGE2) were determined by ELISA (SunRed Tech, Cat N201-12-5292D). The concentrations of IL-2, IL-4, IL-6, IL-10, IL-17, IFN-ɣ, and TNF-α were measured using multiplex flow cytometry bead assay CBA kit (BD Biosciences), acquired with FACSCanto II and FACSDiva v. 1.1.2 software, and analyzed with FCAParray v. 3.0 (BD Biosciences).

Statistical analysis

Significant differences between two groups were evaluated by the *t*-test for unpaired data or Man-Whitney test where appropriate, and ANOVA or Kruskal-Wallis test were applied when comparing 3 groups (GraphPad v. 9).

RESULTS

Stimulated cytokine profiles differ significantly between ATB, LTBI and RC

To evaluate the relative importance of proinflammatory and regulatory cytokines for the instauration and progres-

sion of MTB infection, we compared cytokine secretion potential in response to non-specific stimulation with PHA in LTBI, ATB, and RC groups. While IFN-γ and IL-2 secretion did not differ significantly between ATB and LTBI (mean, pg/ml: 892 vs. 571, and 190 vs. 192, $p>0.05$ for both), ATB patients were characterized by a significantly increased TNF-α (2785 vs. 1568, $p<0.01$), and decreased IL-17 potential (77 vs. 220, $p<0.01$). At the same time, the group of RC was differentiated by a significantly increased expression of IFN-γ (2857) and IL-17 (682) as compared to both ATB and LTBI ($p<0.01$ and $p<0.001$, respectively), increased TNF-α as compared to LTBI (4768 vs. 2785, $p<0.01$), and increased IL-2 as compared to ATB (405.2 vs. 190, $p<0.05$). The potential for IL-6 secretion was significantly decreased in ATB (30 900 vs. 59 000, $p<0.01$), and in RC (17 301 vs. 30 900 and 59 000, $p<0.01$ for both comparisons). At the same time, IL-10 levels were comparable in the three groups (532.1 vs. 710.4 vs. 824.2, ANOVA, $p>0.05$) **(Fig. 1A-F)**. We concluded that a recent contact with MTB activates primarily Th1 and Th17 differentiation accompanied by a well-regulated inflammation.

PGE2/LXA4 balance is violated in the settings of active MTB infection

In addition to cytokines, optimal activation and subsequent adaptive immune response depend on the balance between pro- and anti-inflammatory eicosanoids. Therefore, we further studied LXA4 and PGE2 levels as well as their ratio in the groups of ATB, LTBI, and RC. While the levels of LXA4 and PGE2 did not differ significantly after stimulation **(Figs 2A, 2B)**, the PGE2/LXA4 ratio was significantly increased in ATB (1.9 vs. 1.1, $p<0.01$) **(Fig. 2C)** resulting from both increased mean LXA4 level, and decreased PGE2 level, as compared to LTBI. In addition, we analyzed a subgroup of ATB patients that have completed the standard treatment **(Fig. 2D)**. They were distinguished by significantly decreased levels of LXA4 and PGE2 as compared to non-treated ATB (0.83 vs. 3.42 and 0.73 vs. 6.8, $p<0.001$ for both), and a PGE2/LXA4 ratio similar to LTBI (0.9 vs. 1.1, $p>0.05$). Therefore, we hypothesized that low LXA4 and PGE2, combined with a LXA4/PGE2 ratio close to one might correspond to lower microbial burden, containment, and better prognosis of MTB infection.

Association of PGE2/LXA4 ratio with particular cytokine profiles

Interestingly enough, while LTBI group was homogeneous regarding PGE2/LXA4 ratio, two clearly cut subgroups were observed among RC: with high (mean 2.26) and with low (mean 1.33) PGE2/LXA4 ratio **(Fig. 3A)**. A subgroup with a higher PGE2/LXA4 ratio was also delineated among ATB patients (mean 3.45 vs. 1.37 for the whole group). To further check our hypothesis, we analyzed these subgroups for eventual cytokine profile differences. A PGE2/LXA4 ratio close to one was associated with a significantly higher IL-17 expression among RC, and a higher TNF-α level in ATB subgroup. Based on this, we concluded that RC and ATB donors with PGE2/LXA4 ratio approximating one were closer to the LTBI profile than those with a significantly increased ratio.

DISCUSSION

The need for biomarkers predicting the course of MTB infection, as well as the necessity of specific therapy, is well recognized. Based on the experience with IGRA assays, we and others have concluded that bulk MTB-specific interferon-gamma responses of CD4 and CD8 T cells do not differentiate between MTB stages.[19] A systematic review of the MTB-specific responses of 100 cytokines concluded that the most frequently studied cytokines were IFN-γ, IL-2, TNF-α, IP-10, IL-10, and IL-13 or combinations of them, rendering heterogenous findings and underlining the need for further well-designed studies.[20]

We studied the induced expression of IFN-γ, TNF-α, IL-2, IL-17, IL-6, IL-10 and the lipid mediators PGE2 and LXA4, aiming to discriminate between QFT(-) RC, LTBI, and ATB and, possibly, to predict the course of MTB infection. Our results showed that IL-17 was the best discriminating cytokine differing significantly between each of the studied groups. In addition to high IL-17 expression, RC were differentiated by a high potential for TNF-α, IFN-γ, and IL-2 secretion. In contrast, ATB donors have partially preserved only the ability to produce TNF-α. Importantly, in RC stimulated IL-6 level was significantly lower than in the other groups pointing to preserved regulatory mechanisms at that early point of possible infection.

The key role of IL-17 in the course of TB infection has been related to the early neutrophil-mediated pulmonary inflammatory responses, T cell-mediated IFN-γ production, and granuloma formation in the lung.[9,10] On the other hand, recent data from clinical trials and post-marketing surveillance of biological therapy suggested that IL-17 cells may be dispensable for LTBI control.[21] Our results confirm the exhaustion of Th17 effectors at later stages of MTB infection, in line with a previously demonstrated increase of the Th17-specific inhibitory Treg subset in ATB donors.[19]

The critical role of TNF-α in both early and latent infection has been demonstrated by neutralization of TNF and TNFR in mice, resulting in severe inflammation, uncontrolled infection or reactivation of latent TB infection.[22-24] TNF-α triggers MTB killing by activating phagocytosis in macrophages, promotes dendritic cells maturation, and is responsible for the formation and maintenance of granulomas.[25] While most studies have explored TNF-α expression in ATB and LTBI, a recently published study by Reichler et al. proposed an association of higher baseline TNF-α values with later development of incident TB among contacts.[26]

The precise role of PGE2 and LXA4 in the development of adaptive immunity during human TB remains uncer-

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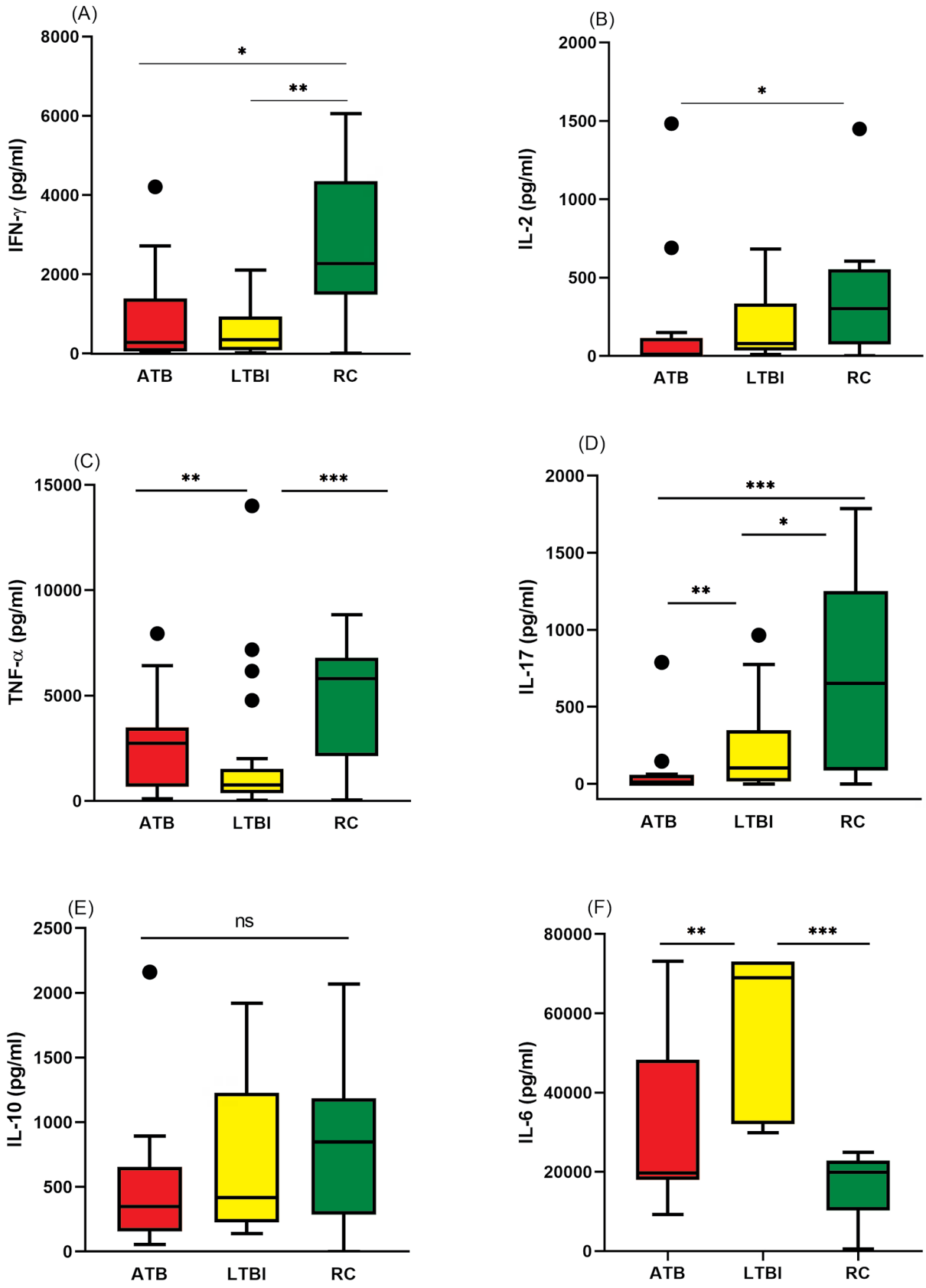

Figure 1. Stimulated cytokine profiles in ATB, LTB, and RC groups. The PHA-stimulated concentrations of IFN-γ (**A**), IL-2 (**B**), TNF-α (**C**), IL-17 (**D**), IL-10 (**E**) and IL-6 (**F**) were measured in ATB (n=15), LTBI (n=22) and RC (n=12) donors. Data is presented as Tukey plots. Boxes and whiskers correspond to 25th - 75th percentile ±1.5 IQR. All values falling out of this interval are shown as dots. *P*-values were calculated using ANOVA test (*** $p<0.001$, ** $p<0.01$, * $p<0.05$).

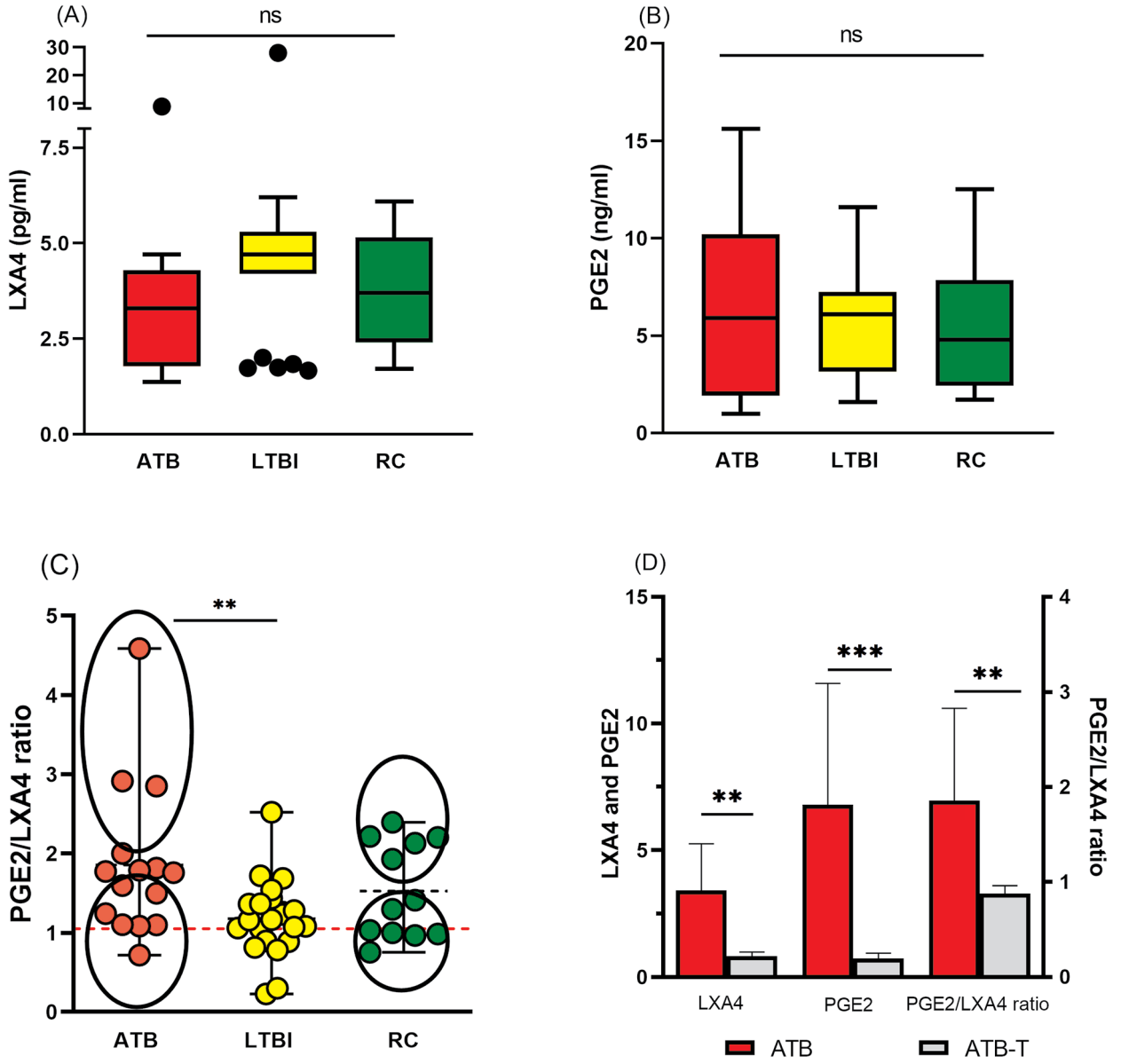

Figure 2. A-D. Stimulated expression of eicosanoids in ATB, LTB and RC groups. The PHA-stimulated concentrations of LXA4 (**A**), PGE2 (**B**) and PGE2/LXA4 (**C**) ratio were measured in ATB (n=15), LTBI (n=22) and RC (n=12) donors. The same parameters were compared between ATB and ATB-T (n=6) (**D**). Data is presented as Tukey plots (**A**, **B**), scatter plot (**C**) with each circle representing a single individual, and column bars (mean+SD). PGE2/LXA4^{high} and PGE2/LXA4^{low} subgroups among RC and ATB donors are encircled. The red dotted line corresponds to the ratio calculated for HC (n=15). *P*-values were calculated using ANOVA test (*** $p<0.001$, ** $p<0.01$, * $p<0.05$, ns = $p>0.05$).

tain. A beneficial role of PGE2 is supported by the facts that PGE synthase-deficient mice and mice lacking the PGE2 receptor EP2 have increased susceptibility to MTB infection.[27,28] On the other hand, high concentrations of PGE2 suppress T cell-mediated immunity against MTB and contribute to the expansion of regulatory T cells.[29]

Lipoxin A4 (LXA4) also modulates innate and adaptive immune responses by exerting either pro-inflammatory or pro-resolution effects.[29-31] Ligation of the lipoxin A4 (LXA4) receptor on neutrophils arrests their migration, but LXA4 is also the dominant lipid mediator produced by macrophages infected with virulent MTB and responsible for induction of necrosis. LXA4 blocks the synthesis of prostaglandin E2 (PGE2), the latter being critical to avoid necrosis. Most probably, the issue of infection is determined by overlapping regulatory networks that function in coordination or antagonism.[15,32]

In our hands, PGE2 and LXA4 did not differ significantly between the studied groups, while their ratio clearly discriminated between situation with high bacterial load as untreated ATB, and contained infection (LTBI, ATB-T). Increased PGE2/LXA4 ratio in the settings of ATB did not

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result from isolated increase of PGE2 or decrease of LXA4 but reflected changes in both mediators, confirming the idea about balanced regulation of proinflammatory and protective lipid mediators. This balance is close to one in the absence of immune activation (healthy controls, LTBI, contained early infection in RC), and is perturbed in the presence of bacterial load and/or inadequate regulation.

Few studies in humans have measured eicosanoid mediators during the stages of TB infection, with somewhat contradictory results. Thus, unlike us, Nore et al. reported increased LXA4 in untreated ATB compared to LTBI, while levels of PGE2 showed no difference between clinical stages of MTB infection and were not affected upon treatment.[18] However, they measured native plasma concentrations and not the stimulated ones. On the other hand, higher levels of total monocytes were observed in ATB, with markedly increased expression of PGE2 and LXA4-specific enzymes upon PPD stimulation. This second model is closer to our stimulation-induced profiles, and the levels of PGE2 and LXA4 detected in our study may reflect induced monocyte production.

In line with us, Kumar et al. described significantly increased plasma levels of LXA4, and PGE2 in TB as compared to healthy controls, as well as significantly increased levels of LXA4 in TB individuals with bilateral or cavitary disease and a higher bacterial burden, while anti-tuberculosis therapy diminished the levels of LXA4 and PGE2.[16] Pellegrini et al. recently showed that PGE2 potently suppresses the MTB-specific immune response by reducing the expression of co-stimulatory receptors (CD80, PDL-1, MHC-II), lymphocyte proliferation, and production of IFN-γ and TNF-α.[33] These results suggest that PGE2 might be attenuating the excessive inflammatory immune response caused by MTB. These findings corroborate with our results showing an increased PGE2/LXA4 ratio in case of active MTB infection (infected RC and ATB). On the other hand, it was shown that a disrupted regulatory interaction between IL-10 and PGE2 leads to excessive expression of PGE2 and impaired killing of intracellular bacteria.[34] That might be the case in ATB where extremely high PGE2/LXA4 ratio was associated with a significantly decreased IL-10 potential **(Fig. 3B)**.

The strong points of our study are the combined evaluation of cytokines and eicosanoid mediators in well-defined groups corresponding to different stages of MTB infection. In addition, we provided data on PGE2/LXA4 ratio in healthy controls. The major limitations in this study are the relatively small size of studied groups, and the cross-sectional design of the study. Further prospective studies following-up recent contacts and reactivated LTB are needed to assess the predictive value of PGE2/LXA4.

CONCLUSIONS

In conclusion, we propose stimulated PGE2/LXA4 ratio as a biomarker sensing the balance between physiological activation that promotes adaptive immunity, and suppression of excessive pathological inflammation. This balance indicates early control of recent infection, and containment of chronic infection in a latent state. A significant increase of PGE2/LXA4 ratio coupled with high IL-10 level signals instauration of infection after a recent contact, while the increased ratio and low TNF-α level point to inefficient granuloma formation in the settings of ATB.

Author contributions

M.N. designed the study, analyzed data, and drafted the manuscript; Y.T. performed the evaluation of PGE2, LXA4, cytokines, and analyzed data; R.E. performed the evalua-

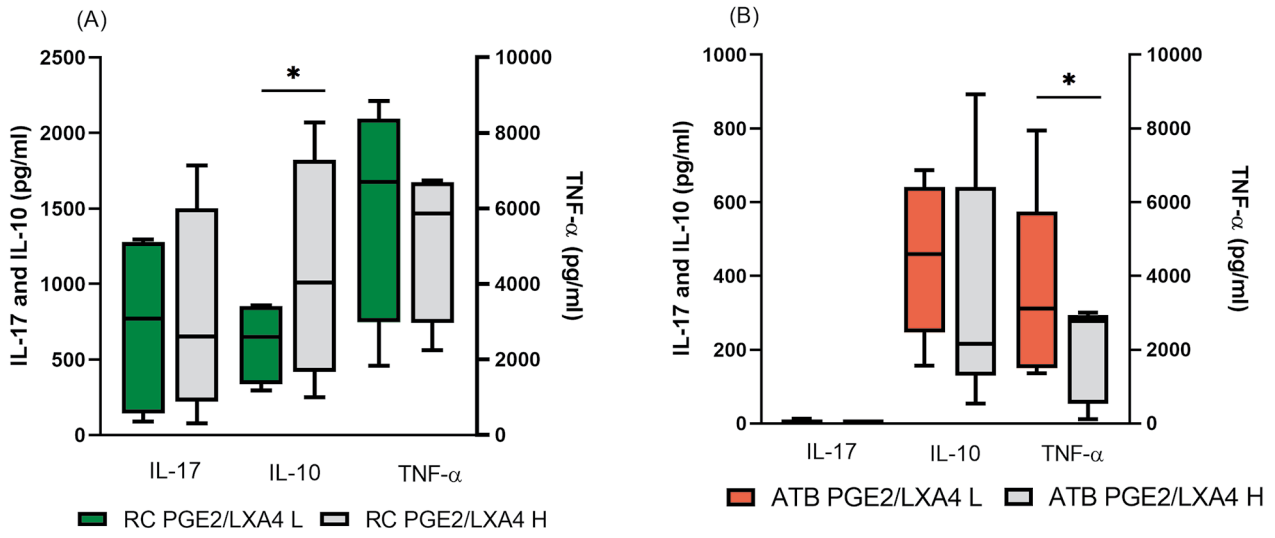

Figure 3. PGE2/LXA4 ratio identifies subgroups with different cytokine potential. PHA-stimulated concentrations of IL-17, IL-10 (left y-axis) and TNF-α (right y-axis) were compared between donors with PGE2/LXA4^{low} and PGE2/LXA4^{high} ratio in the RC group (**A**) and the ATB group (**B**). P-values were calculated using Mann-Whitney test (*** p<0.001, ** p<0.01, * p<0.05, ns = p>0.05).

tion of PGE2, LXA4, cytokines, and analyzed data; V.M. enrolled volunteers, and collected data, E.B., Y.A., and A.B. performed microscopic examinations of AFB, culture examination by liquid (BACTEC - MGIT) and solid (Lowenstein-Jensen) media, and DST by LPA (MBTDR plus).

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Уровни эйкозаноидов и цитокинов различают стадии инфекции MTB

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Резюме

Введение: Потребность в биомаркерах, предсказывающих течение инфекции MTB и необходимость специфической терапии общепризнаны. Последние данные указывают на роль цитокинов и липидных медиаторов в защитном иммунитете против туберкулёза.

Цель: Мы оценили баланс между цитокинами и эйкозаноидами как возможный прогностический показатель при инфекции МТБ.

Материал и методы: Измеряли индуцированную экспрессию эффекторных и регуляторных цитокинов IFN-γ, TNF-α, IL-2, IL-17, IL-6 и IL-10 по отношению к липидным медиаторам PGE2 и LXA4 при активной туберкулёзной. инфекции (ATB, n=15) до и после терапии (ATB-T, n=6), установленной латентной инфекции (LTBI, n=22), недавних контактах с ATB (RC, n=12) и в контрольной группе из здоровых лиц (n=11). Использовали микроматрицу проточной цитометрии (CBA, BD Biosciences) и количественный ELISA (SunRed Tech).

Результаты: Регуляторные цитокины (RC) характеризовались высоким потенциалом секреции IL-17 и цитокинов Th1 в сочетании с низкой экспрессией IL-6, в то время как доноры ATB имели частично сохранённый потенциал TNF-α и более высокую экспрессию IL-6. Соотношение PGE2 к LXA4 различало ситуации с высокой бактериальной нагрузкой (ATB) и локализованной инфекцией (LTBI, ATB-T), а также чётко определяло подгруппы среди доноров RC и ATB.

Заключение: Наши результаты показывают, что повышенное соотношение PGE2/LXA4 в сочетании с высоким уровнем индуцированного IL-10 указывает на инфекцию после недавнего контакта. В условиях ATB повышенное соотношение и низкий уровень TNF-α указывают на неэффективное формирование гранулемы в условиях ATB.

Ключевые слова

эйкозаноиды, IL-17, инфекция MTB, PGE2/LXA4