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The Effects of Immune Memory and Age on Protective Immunity and Tuberculosis Endogenous Reactivation

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Abstract

The WHO objective of eradicating tuberculosis (TB) by 2050 can be achieved by developing more potent anti-TB vaccinations and enhanced preventative medicines against endogenous reactivation of latent TB. What are the factors that lead to a robust memory response after an initial infection? is one of the most important relevant outstanding questions in TB research. ii) How can cytokines contribute to a memory response that is protective against a secondary infection? iii) What are the mechanisms causing the elderly to have a higher risk of reactivation? We looked at a computational model of the immune response to Mycobacterium tuberculosis, which included a mathematical explanation of immunosenescence and the creation and maintenance of immune memory, to try to answer these questions. Key processes governing TB reactivation and immunological memory were identified through the application of sensitivity analysis techniques, thorough model characterization, and in-silico studies. The following model projections sum up the study's key findings: Tumor Necrosis Factor (TNF) levels during primary infection are associated with increased memory protection strength and duration; production of TNF, but not interferon, by memory T cells during secondary infection is a major factor in effective protection; and impaired CD4+ T cell recruitment may encourage the reactivation of latent TB infections in ageing hosts. In this work, immunosenescence and memory are taken into account in an effort to understand the immunological dynamics of a persistent infection over the course of the host's lifetime. Even though the model is particular to tuberculosis, the findings are transferable to other persistent bacterial diseases and can help with the creation, assessment, and improvement of TB treatment and/or immunization regimens.

Keywords: Mycobacterium tuberculosis; Immunology; Single-cell RNA sequencing; Intercellular interactions

Introduction

Toxoplasma gondii, a protozoan parasite that infects around one-third of the world's population, is the cause of the heteroxenous zoonotic disease toxoplasmosis. Additionally, it infects nearly all endothermic creatures. T. gondii infection in humans typically causes an immune-competent person to develop a self-healing illness. In contrast, immunocompromised people experience far more severe infection-related side effects. Animals, particularly sheep, goats, and pigs, are susceptible to toxoplasmosis, which can result in abortion, stillbirth, and neonatal losses. The main way that T. gondii gets into humans is through the consumption of food that has been exposed to the parasite's tissue cysts, like meat from infected animals [1].

Innate immunity's initial line of defense is made up of macrophages, which helps to successfully eradicate T. gondii. This effect is brought about by IL-12, an essential factor in interferon (IFN-) endogenous secretion. Because Th1 cell mediated immunity and IFN- secretion are principally responsible for immunological protection against T. gondii in mice, cellular immune response and production are the most effective technique for the creation of powerful vaccine candidates. Additionally, a number of studies showed a strong correlation between infection with T. gondii and activation or inhibition of the nuclear factor-kappa B (NF-kB) canonical signaling pathway. However, it is still largely unknown how T. gondii and the NF-kB signaling pathway interact [2]. Some molecules interact with NF-kB transcription factors or pertinent effectors, despite the fact that many T. gondii effector molecules have already been reported as powerful immunomodulators. Toxoplasmosis control and prevention techniques must be developed in order to minimise the danger to human health and cattle output. ToxoVax®, produced by Intervet B.V., is the only commercial vaccine currently on the market for reducing the frequency of abortion in sheep. It is based on live attenuated tachyzoites of T. gondii strain S48. Because live vaccines may recover their virulence and cause illness, this vaccine has some restrictions and cannot be used in humans. In addition, the majority of drugs used to treat and control toxoplasmosis are only effective in cases of the disease that are acute, while others, like sulfadoxine/pyremethamine, have extremely toxic side effects on the people who take them, including teratogenic effects and cutaneous lesions. Therefore, it would be very beneficial to prevent this parasitic infection in both humans and animals if a safe and efficient vaccine against T. gondii could be developed [3].

Numerous studies have been conducted on the TgPrx1's molecular and biochemical characteristics. TgPrx1 is expressed in the cytosol and guards against free radicals that are produced as byproducts of essential cytoplasmic functions. Further evidence that TgPrx1 is a potent vaccination antigen and potential therapeutic target comes from the alignment of the amino acid sequence of TgPrx1 with those of numerous other living things. We therefore examined TgPrx1's immunological and protective capabilities in the current work. TgPrx1 research has only been discussed in one study, and no study has yet outlined this antigen's immunoprophylactic potential.

Materials and Methods

The impact of maternal helminth infections on maternal and

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neonatal immunological function and immunity to TB was studied using a cross-sectional methodology. After receiving institutional consent from Addis Ababa University, Armauer Hansen Research Institute, and Mekelle University, this study was carried out in Mekelle, the Tigray regional state, in Northern Ethiopia, from October 2011 to July 2012. Consecutive samples were taken from 85 willing pregnant women in the MCH (Maternal and Child Health) departments of Mekelle Hospital, Semen Health Center, and Ayder Referral Hospital during the final week of their ninth month of pregnancy. The study only included expectant mothers who tested negative for HIV.

Parasitological examination

Stool samples were collected in screw-capped containers and delivered to the Tigray Regional Laboratory for analysis within 30 minutes. Within an hour of collection, duplicate Kato slides were made, and these were evaluated within two days. Within 30 minutes, a wet mount preparation was also carried out to check for hook worm and protozoan infections. All women who tested positive for any kind of parasite after giving birth received the appropriate care [4].

Plasma and CBMC isolation

Through the use of heparinized tubes and 85 full-terms, healthy pregnancies, cord blood was obtained. Cord blood was drawn straight from the umbilical cord vein using a needle connected with a 20 ml syringe to prevent contamination with maternal blood. Plasma was separated by centrifugation for 10 minutes at 1500 rpm, and it was then kept at 80°C until it was taken to the AHRI lab. CBMCs were isolated using the Ficoll-Hypaque density gradient technique, washed three times with complete media, and then kept frozen in freezing medium (10% dimethyl sulfoxide (DMSO) in FCS) at 80°C. The cord blood was diluted 1:1 with complete media (RPMI containing 10% foetal calf serum (FCS), 1% Penicillin and Streptomycin (P/S), and 1% L-glutamine).

Total IgE ELISA assay

Human total IgE ELISA kits were used to perform ELISA after plasma was thawed (product code 3810-1H-6, Mabtech, Sweden). The anti-total IgE monoclonal antibody (mAb 107) was coated onto microwell plates and left to sit overnight at 4°C. 100 l/well of plasma and the serially diluted standards were added to the wells in accordance with the plate layout after plates had been blocked by adding 200 l/well of 0.05% PBS Tween 20 containing 0.1% BSA and being incubated for an hour at room temperature. After adding a 11000 dilution of streptavidin-HRP, a biotinylated monoclonal detection antibody was added and incubated for 1 hour. Wells were cleaned five times with PBS containing 0.05% Tween 20 at each step. For color development, a tablet of O-phenylenediaminedihydrochloride (OPD) was employed as the substrate. On an ELISA reader for multiwall plates, ODs were measured at 450 nm. The total IgE concentration values were obtained by converting the ODs using GraphPad PRISM statistical programme, Inc., USA.

TB specific IgG ELISA assay

The Diagnostic Automation Mycobacterium tuberculosis IgG antibody test kit was used to conduct a TB-specific IgG ELISA. The wells of the microtiter strips coated with M. tuberculosis antigens were pipetted with sample plasma that had been diluted 1101 or ready-to-use standards. The ready-to-use anti-human-IgG peroxidase conjugate was added after an hour of incubation and incubated for 30 minutes. The substrate (TMB) solution was pipetted after washing, and it was then incubated for 20 minutes. By adding stop solution, the color development was stopped, and the wavelength of 450 nm was used to take spectrophotometric measurements.

Statistical analysis

The 19th version of the SPSS statistical package was used to enter and analyses the data. Socio-demographic and clinical characteristics were subjected to descriptive statistical analysis. Total IgE ODs were converted to real concentration using GraphPad PRISM. In order to investigate the relationship between the QFT-GIT indeterminate result and other clinical variables, univariate logistic regression was performed. The relationship between demographic risk factors (age, occupation, educational attainment, and number of pregnancies) and parasite diseases was investigated using multivariate analysis [5]. To calculate the mean difference of total IgE in QFT-GIT positive, negative, and indeterminate results, one way ANOVA was utilised. The helminth positive and negative results from the QFT-GIT were compared with each other using the chi square test. Statistics were utilised to assess the variations in cord blood plasma total IgE between helminth positive and negative samples using independent sample t-tests. Nonparametric statistical analysis was utilised since the frequencies of cytokine-secreting CBMCs were not regularly distributed. In order to compare the frequencies of IFN- and IL-4 CBMCs among the four different groups, Kruskal-Wallis and Mann-Whitney tests were utilised. In order to ascertain the relationship between the frequencies of IFN- and IL-4 secreting CBMCs and total IgE values, the Spearman Rank Order Correlation coefficient was also applied. Following the division of study participants into groups depending on their helminth and latent TB infection status, the immune response was analysed. There were four groups as a result: helminth positive-LTBI positive (n = 9); helminth positive-LTBI negative (n = 14); helminth negative-LTBI positive (n = 13); and helminth negative-LTBI negative (n = 35).

Results

Demographic and clinical information

Participants in the study had a 25-year median age (IQR 22, 28). Primary school made up 43 (50.6%) of the study participants' educational history, followed by high school (24), tertiary school (9), and no formal education (9). The study's participants were all city dwellers. Housewives made up the majority of survey participants (83.3%), while government workers made up 11.8%.

Of the study's participants, 40 (47%) were expecting their first child, while 25 (29.4%) were expecting their second. Only 13 (or 15.3%) of the total participants reported having had the BCG vaccine, and only 20 (or 23.1%) of those participants had a BCG scar. Only five survey participants admitted to having had close contact with a TB patient, and each of these encounters took place between five and ten years prior [6].

Parasitic infections

For helminths and protozoans, the prevalence of parasitic illnesses was 27.1% (n = 23) and 8.2% (n = 7), respectively. Schistosoma mansoni (20.0%, n = 17) was the most prevalent parasite, followed by Ascaris lumboricoid (8.2%, n = 7), Entrobius vermicularis (5.8%, n = 5), Trichuris trichiura (4.7%, n = 4), Hymenolepis nana (2.3%, n = 2), Entamoeba species (8.2%, n = 7), and Schistosomia haematobium was not discovered in any of the study participants. 28.2% of people had intestinal parasites overall. 15.3% of the study participants had infection with more than one helminth. Infection with both helminths

and protozoa was seen in 7.1% of the study participants.

Multivariate analysis was used to test the relationship between demographic risk factors (age, occupation, educational attainment, and number of pregnancies) and parasitic infections. Only the relationship between educational attainment and parasitic infection was found to be statistically significant. The risks of parasite infection dropped as education levels rose from no formal schooling to basic and subsequently secondary level (OR = 0.50, CI = 0.211 to 0.992, p = 0.048).

Latent tuberculosis infection

LTBI was discovered in 22 (26.7%) of the QFT-GIT test subjects, while 14 (17%) had an ambiguous result. When three of the ambiguous samples were randomly chosen and the test's repeatability was checked again, the results showed that they were still indeterminate [7, 8]. An inadequate IFN- response to the mitogen was the cause of all undecided outcomes. As compared to helminth negative participants, the proportion of QFT-GIT indeterminate results was considerably greater in helminth positive participants (p = 0.048), while this effect was not seen in protozoan infection (p = 0.273).

Total white cell count (wbc) and differential count in cord blood

The cord blood's median WBC was 13440/mm3 (IQR: 11575–16178). Further research revealed no statistically significant difference in the median cord blood WBC count between study participants who were helminth positive and those who were not (p = 0.714). Similarly, maternal helminth infection had no impact on the number of lymphocytes, monocytes, or granulocytes in the cord blood [9].

Total IgE in Cord Blood

The mean cord blood total IgE level was significantly lower in helminth-negative subjects than in helminth-positive subjects (0.760.59, p = 0.042, t-test). None of the helminth species demonstrated statistically significant differences, despite the fact that the overall effect of maternal helminth infection was achieved at a significant level of p0.05.

TB specific igg

Regardless of their QFT results, TB specific IgG ELISAs were carried out on 82 research participants to see if maternal helminth infections and higher cord blood IgE had a relationship with the cross-placental transfer of TB specific IgG [10]. The findings demonstrated that 6 (7.3%) of the cord blood samples had TB-specific IgG levels above the threshold (Mycobacterium tuberculosis IgG, Diagnosis Automation, Inc, catalogue number 5111-8, USA). Those who were helminth negative (12.35.1) had a significantly lower mean concentration of TB specific IgG in cord blood than those who were positive (21.97.9) (p = 0.002). We also looked at the cord blood plasma's total IgE and TB-specific IgG concentrations. The findings revealed a moderately positive statistically significant correlation between cord blood's total IgE and TB-specific IgG (r = 0.34, p = 0.034).

ELISpot Assay

After CBMCs were stimulated with TB antigens, in vitro IFN- and IL-4 secretion was assessed using an ELISpot test, and results were expressed as spot forming cells (SFC)/million cells. Samples having anti-CD3 positive control cytokine responses that were lower than the reaction to Mycobacterium antigens were not included in the analysis. 22 study participants, including [helminth and LTBI co-infected people (H+L+, n = 9), and helminth negative but LTBI positive subjects (HL+, n = 13), were compared for the frequency of IFN- and IL-4 cytokine responses in the CBMCs. In response to ESAT-6/CFP-10 cocktail and PPD in vitro stimulation, the median frequency of IFN-spot producing CBMCs was 43 (IQR = 19 to 119), 58 (IQR = 29 to 123) for H+L+, and 120 (IQR = 54 to 231) and 123 (IQR = 67 to 265) for HL+.

However, the difference in the median frequency of IL-4-secreting CBMCs between helminth-negative and -positive cells was unaffected by the stimulation of ESAT-6/CFP-10 (p = 0.64) and PPD (p = 0.38), respectively.

Using a different Spearman Rank Order Correlation coefficient, the association between the ESAT-6/CFP-10 cocktail and total IgE stimulation of the cord blood's PPD on IFN-secreting CBMCs was also examined. The frequency of IFN-secreting cells in response to ESAT-6/CFP-10 cocktail (rs = 0.35) and PPD (rs = 0.41) stimulation and the concentration of total IgE in cord blood were significantly correlated in the helminth positive and helminth negative research participants, respectively [11].

Discussion

A significant virus-targeting HIV intervention is HAART. Although HAART is effective at stopping HIV replication, it can only partially lower chronic immune activation and reverse the immunological dysregulation that is present in treated people. Tat has significant impacts on the virus and the immune system and is constantly produced in cell reservoirs even under HAART, leading us to speculate that Tat is a crucial component for disease maintenance in drug-treated patients.

Here, we demonstrate how therapeutic immunisation with Tat further lowers the immune activation that is still present under HAART and is also evident in these OBS subjects. In instance, CD38+/CD8+ T cells significantly decreased in Tat-immunized people, especially at the 30 g dose, and this decrease was inversely correlated with anti-Tat IgA titers, central memory CD8+ T cells, and IL-2 production in response to Tat.

Additionally, while co-expression of DR and CD38 on CD8+ T cells has been widely documented to be linked to immunological activation in HIV progression, it is also present on immature and quickly cycling T cells. This shows that the restoration of homeostatic systems following therapeutic immunisation with Tat may potentially result in co-expression of DR and CD38 [12, 13]. The rise in CD4+ and CD8+ central memory T cells and the recovery of T cell responses to HIV and recall antigens that were seen in vaccine recipients are both compatible with this scenario. Therefore, it is tempting to hypothesise that Tat immunisation facilitates the restoration of appropriate and effective immune responses by lowering the energy associated with immunological dysregulation brought on by HIV. This could account for the seemingly paradoxical rise in doubly positive (CD38+/DR+) activated CD8+ T cells despite a concurrent decline in other soluble and cellular inflammation and immune activation markers, such as CD38+/DR+ CD4+ T cells, and an increase in both T-regs and central memory CD8+ T cells [14].

The consistent increases in the percentage and absolute numbers of CD4+ T cells and B lymphocytes as well as the decrease in the proportion of CD8+ T cells and NK lymphocytes were connected with the rise in T-reg and the decline in immune activation. The CD4/CD8 T cell ratio therefore gradually rose. Such a pattern of T and B cell

"repopulation" contrasts noticeably from that which has been observed here in the OBS group and has been reported to occur during HAART.

Of note, Tat immunisation showed the same effects regardless of the type of therapy, indicating that Tat can enhance various HAART regimens, despite differences being seen in the percentage of lymphocyte subsets with different HAART regimens (NNRTI-based versus PI-based) in the OBS individuals [15].

Conclusions

The increase or de novo emergence of cellular adaptive immune responses to HIV Env or to recall antigens in such a situation shows that restoration of important immunological parameters occurs after Tat immunisation. In actuality, these outcomes were linked to a rise in CD4+ and CD8+ functional effector memory and central memory T cells, as well as a decrease in their terminally-differentiated and functionally-exhausted counterparts. This is in contrast to the trend found in HIV-treated illness (and also shown in OBS), where effector memory T cells continue to be continuously elevated and central memory CD4+ and CD8+ T cell subsets are only partially restored.

The effects of vaccination were long-lasting since, after 48 weeks from the initial immunisation, they were still present or even enhanced, with the exception of the reduction of CD38 on CD8+ T cells and CD25 on CD4+ T cells.

According to the data, HAART and Tat vaccination work together to help reestablish immunological homeostasis. In fact, in those individuals who had higher immunological dysregulation at baseline, the therapeutic effects of Tat immunisation were more prominent.

Information on the necessity for the timing of immunizations will be available from the prolonged follow-up of the vaccinations boosting.

Conflict of Interest

None

Acknowledgement

None

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