IL-21 ALTERS TFH DYNAMICS, IMPROVES FLU VACCINE RESPONSE IN OLD SIV+ NHPS UNDER ART

AIMS

Hypothetical contribution to infaraging (chronic low-grade systemic infectious) and immune senescence (accelerated aging of the immune system). Immune dysfunction, in the form of impaired antibody (Ab) responses to vaccines such as influenza (Flu) vaccination, is observed in aging and HIV infection. Since the central role of IL-21 in Ab responses was hypothesized that administration of IL-21 in a flu vaccine-adjacent in aged ART treated, SIV+ Rhesus Macaques (RM) would result in significant improvement in the quality of pTfh and B cell function and improved germinal center reactions, resulting in improved Ab responses to vaccination.

BACKGROUND

Wiring contributes to infaraging (chronic low-grade systemic infectious) and immune senescence (accelerated aging of the immune system) (26). Immune dysfunction, in the form of impaired antibody (Ab) responses to vaccines such as influenza (Flu) vaccination, is observed in aging and HIV infection. IL-21 is critical in the generation and function of CD4+ T follicular helper (Tfh) cells, which provide cognate help to B cells for high-affinity antibody production (12,13)

HYPOTHESIS

Administration of IL-21 as a flu vaccine-adjacent in aged ART treated, SIV+ Rhesus Macaques (RM) would result in significant improvement in the quality of pTfh and B cell function along with improved germinal center reactions, resulting in improved Ab responses to vaccination.

METHODS

Flu vaccination was administered with and without subcutaneous IL-21 in a prime, boost, booster series at 3-month intervals to old ART treated, SIV+ (SRvNL4-3) RM. IL-21 was given (500µg) on d0, d2, d5, post each vaccine dose. Blood was collected on d0, d5, d14, and d42, and lymph node tissue was collected on d14 after each vaccine dose. Serum was analyzed for flu Ab titers, and PBMC with multicolor flow cytometry using panels for CXCR5+ expression on CD4+ T central memory (CD95+CD28+CD4+CD3+, live cells) and Tfh. Serum was analyzed for flu Ab titers, and PBMC with multicolor flow cytometry using panels for CXCR5+ expression on CD4+ T central memory (CD95+CD28+CD4+CD3+, live cells) and Tfh.

RESULTS

HAI titers highlight age-associated immune impairment and IL-21 induced improvement of Ab responses

Titers increased in IL-21 treated animals from 1:100 at baseline to 1:283 post boost 1 (PB1) and were significantly higher compared to non-IL-21 treated animals (mean=1:100) (Fig. 3B). These findings suggest IL-21 has a significant adverse effect, improving flu vaccine-adjacent in aged RM. As no baseline IL-21 differences were observed, these results highlight that IL-21 may be directly or indirectly inducing a shift in a pTfh phenotype and thereby, warranting further investigation on a systemic-adverse effect.

MULTICOLOR FLOW CYTOMETRY

Analysis of pTfh reveals association between pTfh expansion and Ab response to vaccination

No significant differences in pTfh frequency between groups (Fig. 3A). Pre- vs post-IL-21 HAI titers of controls (mean±SD) did not differ from IL-21 treated animals (mean±1SD) (Fig. 3B). Interestingly, IL-21 treated animals from 1:100 baseline to 1:283 post boost 1 (PB1) and were significantly higher than the PB1 control mean titer of 1:60 (Fig. 3B).

RESULTS (cont.)

Th (CD4+PD1+) density per LN cell follicle was significantly higher in IL-21 treated animals compared to unboosted (Fig. 5A).

Correlation analysis revealed a significant association between average follicular Tfh cell density per follicle and HAI titers (Fig. 5B).

Further, the density of IL-21+ cells per follicle was significantly higher in IL-21 treated animals compared to unboosted (Fig. 5C).

SUMMARY

• No baseline differences were observed in pTfh frequency nor HAI titers.
• IL-21 treated old, ART treated, SIV+ RM have improved HAI titers
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REFERENCES


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