DIMINISHED IMMUNE IMPRINTING AT THE UPPER RESPIRATORY TRACT FOLLOWING SARS-COV-2 BREAKTHROUGH INFECTION

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BACKGROUND

Immune imprinting, also known as original antigenic sin, refers to the effects prior exposures have on subsequent immunity against antigenically related viruses. The immune imprinting of humoral immunity at anatomic sites of the respiratory tract following SARS-CoV-2 breakthrough infection is not well understood.

METHODS

Ninety-six adult donors with COVID-19 vaccination and breakthrough infection (BTI) during the BA.5 wave were recruited for this study. Blood samples and paired swabs, including nasal swabs from the midpoint of the inferior turbinate (MT) and nasopharyngeal (NP) swabs were collected. Each sample was monitored via a pseudovirus-based virus neutralization assay to determine neutralizing antibody (NAb) titers against wild-type (WT), BA.5 and XBB variants. The samples with detectable NAb titers were included for further analyses on immune imprinting level. Antigenic cartography was generated based on the NAb data. B cell immunophenotyping was assessed by multiparameter flow cytometry.

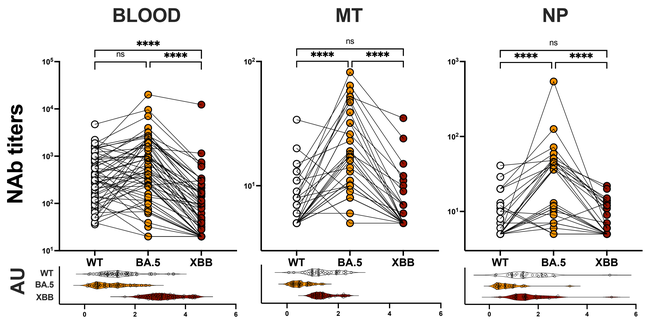


Figure 1. NAb titers against WT, BA.5 and XBB in blood and mucosal samples from the vaccinated subjects with BTI. The antigenic unit (AU) corresponding to fold change in NAb titers.

Distinct antibody profiles observed in the upper respiratory tract, compared to the circulating system, suggest reduced immune imprinting of respiratory mucosal immunity following SARS-CoV-2 breakthrough infection.

RESULTS

These vaccinated subjects with BTI showed significantly higher levels of circulating NAbs against WT (4.2-fold) and BA.5 (6.7-fold) than against XBB (P<0.0001 for both), while exhibiting roughly similar NAb titers against WT and BA.5 in circulation (<2-fold difference) (Fig.1). Mucosal NAb responses from MT and NP samples were highly correlated (P=0.003), and displayed distinct profiles compared to circulating antibodies. Both MT and NP samples showed significantly higher mucosal NAb titers against BA.5 than that against WT (2.5-fold and 2.4- fold, respectively; P<0.0001 for both), and against XBB (2.6-fold and 2.7-fold, respectively; P<0.0001 for both) (Fig.1). Additionally, the antigenic distances from WT to BA.5 or to XBB were discernibly reduced in respiratory mucosal profile compared to that in circulation (P<0.05 for all) (Fig.1). Germinal center B cells targeting BA.5 were detectable in the majority of NP samples but were barely observed in MT samples (Fig.2). There was also a trend of higher BA.5-specific memory B cells in NP samples, predominantly displaying a resting memory phenotype (Fig.2).

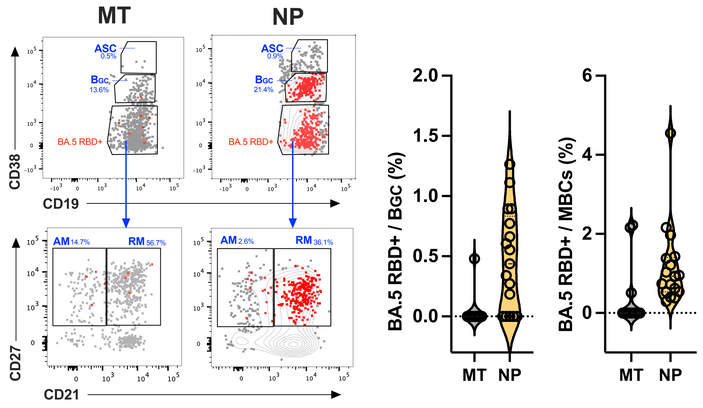


Figure 2. Germinal center B cells (B_{GC}) and memory B cells (MBCs) (activated/resting MBC, AM/RM) responding to BA.5 in MT and NP samples from the vaccinated subjects with BTI .

CONCLUSIONS

The distinct antibody profiles between the upper respiratory tract and the circulating system reveal diminished immune imprinting at the upper respiratory tract, evidenced by the enhanced BA.5-specific mucosal NAb response following BTI during the BA.5 wave. These findings have important implications for our understanding of respiratory mucosal immunity against evolving SARS-CoV-2.

ADDITIONAL KEY INFORMATION

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