Autophagy regulates somatic mutagenesis via Lamin B1-dependent mechanism

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Autophagy is a membrane trafficking process that degrades cellular cytoplasmic and nuclear components. Its alteration in germinal center B cells affects the germinal center reaction, ultimately influencing B cell differentiation and fate[1,2,3,4]. However, specific mechanisms linking autophagy and development of effective primary immune responses have not been thoroughly described.
Previous reports demonstrated that nuclear lamina is a *bona fide* substrate for autophagic machinery, suggesting a functional link between autophagy and the lamina-mediated epigenetic regulation[5]. Within the immune context, we observed that Lamin B1 protein downregulation in germinal centers provide regulatory access of the somatic hypermutation machinery to immunoglobulin heavy variable (IGHV) loci[6].

Therefore, capitalizing on our previous findings, here we report that nuclear autophagy plays a role in germinal center B cell reprogramming during the normal adaptive immune response via Lamin B1 dependent mechanism.

Genetic or pharmacological autophagy inhibition during centroblast and centrocyte stage abrogated the *de novo* targeted mutagenesis within the IGHV loci. These functional alterations coincided with observable changes in Lamin B1 nuclear topology, as detected by super resolution localization microscopy. In particular, we noticed a significant reshaping in chromatin accessibility profile, analyzed at single-cell resolution level, in the ATG7-deficient germinal center B cell population.

Furthermore, single-cell transcriptomics confirmed that inhibition of autophagy impaired gene expression at the peak and end of the germinal center reaction. Downstream functional experiments showed that antibody-secreting cells, originating from autophagy-deficient germinal center B cells, reduced immunoglobulin affinity, due to defective germinal center somatic hypermutation.

Taken together, our data indicate that nuclear autophagy is directly involved in humoral immunity by regulating nuclear dynamics and somatic mutagenesis in germinal center B cells. This evidence consolidates autophagy as an upstream regulator of primary nucleotide substitution and an essential player in regulating Lamin B1 controlled genes.

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