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The origin of pre-plasmablastic cells

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Abstract:

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The origin of pre-plasmablastic cells

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In this issue of Blood, Pignarre A et al. characterize the genomic events involved in the cell fate decision between activated B cells and plasmablast¹. Plasma cells play an important role in humoral immunity by synthesizing and secreting antibodies². Understanding the biological processes that control the production of plasma cells is critical both to ensure efficient immune response without autoimmunity or immune deficiency and prevent tumorigenesis. The production of IL-4 by follicular helper T cells drives B cell amplification and maturation³. However, the full molecular mechanisms behind these functions are not fully understood. Pignarre A et al. reported new biological events driving normal B to plasma cell differentiation. Using an *in vitro* model, naïve B cells are cultured in a two-step process which results in differentiation into plasmablasts⁴, they demonstrated that cells that are destined to differentiate into plasma cells if there is an early response to IL-4, which results in downregulation of the CD23 cell surface protein and IL-4/STAT6 signaling. However, B cells maintaining IL-4 signaling did not differentiate. Furthermore, the differentiation of CD23 negative cells is associated with CBLb E3 ubiquitin ligase downregulation, coinciding with IRF4 induction and with specific chromatin and transcriptional **modifications**. The changes were identified by ATAC-sequencing and hydroxymethylation profiling. However, no major changes in expression of epigenetic factors was noted. CBLb is known to prevent premature germinal center (GC) exit

promoting IRF4 degradation in light zone B cells⁵. Pignarre et al. reported potential STAT6 binding sites in the CBLb promoter suggesting potential direct regulation, hence the interest in characterizing STAT6 targets using chromatin immunoprecipitation. CD23 negative B cells, post activation, have the characteristics of preplasmablasts with a significant increase in chromatin accessibility at immunoglobulin heavy chains coding loci. Full transcriptomic characterization of the proposed model at a single-cell level would be particularly useful in deciphering the heterogeneity and transcriptional trajectories during B to plasma cell differentiation. The major transcriptional and epigenetic changes reported by Pignarre et al. may be associated with changes in nuclear organization during terminal B cell differentiation. Gene regulation depends on the 3-dimensional chromatin organization and its regulatory elements. Recent data obtained in a mouse model revealed that B to plasma cell differentiation is associated with major changes in chromosome topology that could be driven by plasma cell biology or reflect enhancer-induced modifications in chromatin organization⁶. B to plasma cell transition is associated with compartmentalization changes along with **gain in genomic interactions across the Prdm1 locus increasing genomic interactions between promoter regions and regulatory elements, concurrent with transcriptional induction. In contrast, early B-cell factor 1 (Ebf1) locus repositions to peri-centromeric heterochromatin in association with transcriptional repression.** Furthermore, the inter-chromosomal hubs reported during B to plasma cell maturation are associated with histone marks that define transcriptionally active or repressive hubs. The epigenetic landscape characterization together with nuclear architecture study of the human B to PC differentiation model developed by Pignarre et al. may provide important findings to progress in the understanding of the molecular mechanisms driving B to plasma cell fate.

IL-4 production by T follicular helper and STAT6 mutations activate and drive the IL4/STAT6 axis in follicular lymphoma⁷. Recently, single-cell characterization of germinal center B cells generated a new single-cell cell of origin classification that identified distinct prognostic subgroups within the GCB and ABC diffuse large B cell lymphoma subgroups⁸. The analysis of these single-cell transcriptomic resources derived from germinal center purified B cells, in light of the new data provided by Pignarre et al. may be of particular interest. The results provided by Pignarre et al. provide new insights in the molecular mechanisms driving follicular lymphoma biology.

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Figure legend

After activation, B cells that are committed to differentiate into plasma cells downregulate the CD23 cell surface protein, IL-4/STAT6 signaling and CBLb activity concomitantly with IRF4 induction. B cells that maintain the IL-4 signaling will not differentiate.

