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ORAL ABSTRACTS

603.LYMPHOID ONCOGENESIS: BASIC

SWI/SNF Chromatin Remodeling Complex Orchestrates Sequential Binding of Key Transcription Factors in B Cells and Restricts Aggressive Lymphoma

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Mutations in the SWI/SNF chromatin remodeling complex BAF are a recurring feature in many cancers, with a high prevalence in follicular lymphoma (FL; >19%) and diffuse large B-cell lymphoma (DLBCL; >34%). Despite this, the mechanism that links mutations in *ARID1A*, most frequently mutated BAF subunit, to the development of lymphoma is still not understood.
To this aim, we crossed *Arid1a*-floxed mice with *Cγ1*-Cre mice to yield offspring with a conditional (cKO) *Arid1a* deletion in germinal center (GC) B cells, FL and DLBCL cell-of-origin. We immunized WT/WT (*Arid1a*+/+; *Cγ1*Cre/+) and cKO/WT (*Arid1a*+/-; *Cγ1*Cre/+) mice with sheep red blood cells and analyzed 10 days later at the peak of the GC reaction. Upon *Arid1a* deletion, we found a decrease in the total number of GC B cells relative to total B cells (WT/WT vs. cKO/WT; p<0.001). However, we observed skewing of GC polarity manifesting as increased proportions of proliferating centroblasts (CB) vs. centrocytes (CC) (WT/WT vs. cKO/WT; p=0.004). These observations imply a substantial dysfunction at the CC stage, which could account for the overall reduced number of GC B-cells. To investigate this, we performed a detailed molecular characterization of these cells.
We performed the ATAC-seq assay on sorted CB and CC from our mouse model and observed an extensive loss of chromatin accessibility. Changes in chromatin accessibility are thought to be dependent on the recruitment of the BAF complex by specific transcription factors. We discovered strong enrichment for DNA motifs of PU.1 and NF-kB factors in closing chromatin (p-value <0.001), indicating their dependence on the BAF complex. Furthermore, we noted that this chromatin closing occurred in proximity to canonical GC exit programs, including genes induced by the CD40, NF-kB signaling, IRF4, STAT3, IL2, IL4, IL6 and Notch pathways (hypergeometric p-value <0.001), indicating GC-exit perturbation.
Expanding upon our findings, we leveraged a combined single-cell RNA and ATAC assay (Multiome) to scrutinize subtle shifts within GC populations. Determining the chromatin accessibility within the pseudo-time trajectory of GC transitions, we found that PU.1 and NF-kB factors are chronologically dependent on ARID1A with PU.1 accessibility initially compromised, followed by a subsequent decrease at binding sites for NF-kB factors. This sequence reveals ARID1A's unrecognized function as a regulator of temporal dynamics of these key transcription factors. Strikingly, our Multiome data revealed expansion of the pre-memory B cells accompanied by a decrease in the proportion of pre-plasma cells upon *Arid1a* deletion (p-value <0.001), suggesting that *Arid1a* loss favors GC exit towards the memory cell fate. To validate our findings, we performed immunophenotyping and observed an increase in memory B cells in cKO/WT mice (p=0.019), and a decrease in long-lived

plasma cells (p=0.012) upon NP-KLH immunization. Furthermore, we observed that the absence of ARID1A tilts GC cell-fate towards immature IgM+CD80-PDL2- memory B cells (p=0.0016), known for their potential to re-enter new GCs.
Linking this critical role of ARID1A in chromatin regulation to lymphomagenesis, we observed a reduction in overall survival for mice carrying *VavP-Bcl2*; *Arid1a*+/- allele (compared to *VavP-Bcl2*; *Arid1a*+/+; p=0.0087). Remarkably, we further show that FL patients with *ARID1A*-inactivating mutations display an immature memory B-cell-like state with increased transformation risk to aggressive disease (p=0.0391). These observations offer mechanistic understanding into the emergence of both indolent and aggressive lymphomas in ARID1A-mutant patients through formation of immature memory-like clonal precursors.

Disclosures Chadburn: *Leica Biosystems:* Consultancy; *Boehringer Ingelheim Pharmaceuticals, Inc.:* Consultancy; *Medical College of Wisconsin:* Honoraria. **Steidl:** *Seattle Genetics, AbbVie, and Bayer:* Consultancy; *Bristol Myers Squibb, Epizyme and Trillium Therapeutics Inc.:* Research Funding. **Scott:** *Janssen and Roche:* Research Funding; *Abbvie, AstraZeneca, Incyte:* Consultancy. **Mason:** *Biotia and Onegevity Health:* Membership on an entity's Board of Directors or advisory committees; *Abbvie, ArcBio, Daiichi Sankyo, DNA Genotek, Tempus Labs, and Whole Biome:* Other: an advisor or grantee. **Green:** *KDAc Therapeutics:* Current equity holder in private company; *Sanofi:* Research Funding; *Abbvie:* Honoraria; *Abbvie:* Research Funding; *Kite/Gilead:* Research Funding; *Allogene:* Research Funding; *BMS:* Consultancy; *Daiichi Sankyo:* Honoraria. **Melnick:** *Ipsen:* Consultancy, Research Funding; *Treeline Biosciences:* Consultancy; *Janssen:* Research Funding; *Daiichi Sankyo:* Consultancy, Research Funding.

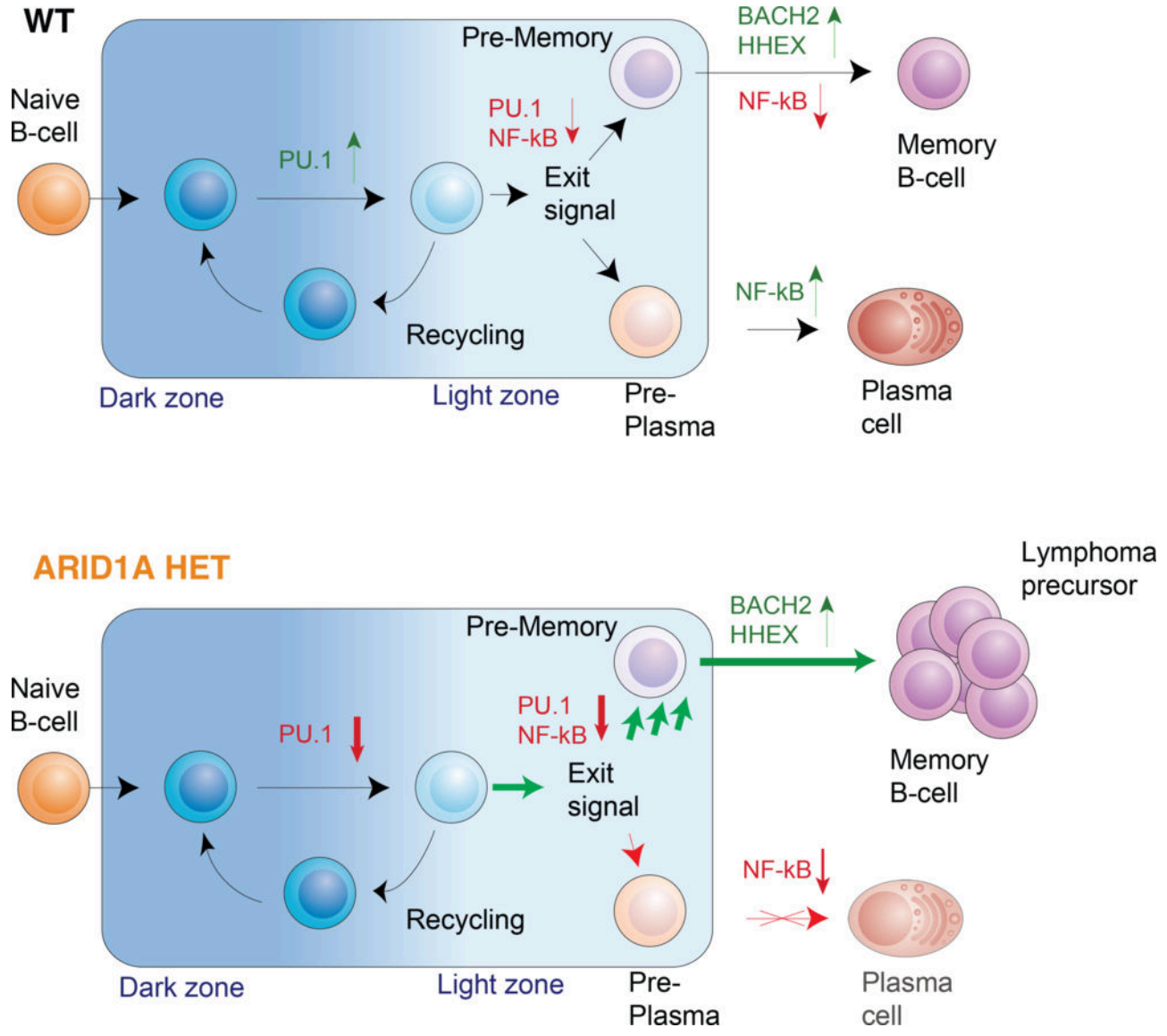

Figure 1

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