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Science perspective- B cell division leads to antigen feast or famine

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Humoral immunity is critical for host defense and depends upon the generation of secreted antibodies with high affinity for antigens. The generation of high affinity antibodies is a Darwinian process in which cycles of antibody gene mutation and selection for antigen binding lead to many-fold increases of antibody affinity. In this issue of Science, Thauat et al report that B cells (BCs) inherit antigen in an asymmetric manner during cell division, leaving all but one daughter cell starved of antigen ([1](#)) while the cells are otherwise dividing symmetrically based on partitioning of the ancestral polarity protein PKC- ζ . This previously unimagined result has implications for models of the humoral response that we can begin to probe here.

The cell biology of antigen handling by BCs is well studied due to its central importance in humoral responses. BCs use their antibodies as receptor to deliver antigen to internal organelles with MHC class II molecules that bind antigen derived peptides and present these to T cells ([2-5](#))(Figure 1A). The organelle in which antigen and MHC class II meet has been referred to as the MHC class II compartment (MIIC). The MIIC served as a “timed-release” system such that an antigen depot is maintained over a period of days. Thauat et al demonstrate using imaging cytometry that the MIIC is largely indivisible and is often inherited entirely by one daughter cell during mitosis ([1](#)) (Figure 1B). This means that most daughters suffer antigen famine and are perfectly prepared to mutate their receptors and then will only survive if a high affinity antibody is generated that can capture more antigen. The single daughter that feasts on the MIIC can continue to receive help from T cells without a need for new antigen capture, which is not compatible with an effective natural selection scheme and suggests this cell has a different fate.

The anatomic site in which high affinity antibodies are made is the germinal center (GC). In iterative cycles, BCs divide and mutate their receptors and subsequently acquire antigen from follicular dendritic cells to get selected by T follicular helper cells (TFH). Plasma cells (PCs) are generated throughout the course of a humoral response with short lived PCs arising prior to GC formation ([6](#)) and long-lived PCs generated during the GC reaction ([7](#)). GC BCs express the master regulator Bcl6, whereas PCs express the master regulator Blimp1 ([8](#)). In addition to containing antigen, the MIIC activates Erk and Akt kinases ([9](#)). Akt represses Bcl6 and activation induced cytosine deaminase, which is required to mutate antibody genes ([10](#)), whereas Erk activation is required for Blimp-1 expression ([11](#)). While the

consequences of MIIC signaling need to be tested more directly in this setting, we can incorporate rules based on these observations into mathematical models.

It was predicted by mathematical models ([12](#)) and verified by experiments ([13](#), [14](#)) that help by TFH is a critical and limiting factor for BC selection. We can modify this base model ([15](#)) to incorporate additional rules based on asymmetric MIIC inheritance. Thauinat et al demonstrated that the daughter cell inheriting MIIC can undergo additional interactions with TFH ([1](#)) without further antigen collection (Figure 1C, model M1). However, the actual fate of MIIC inheriting BCs in germinal centers is not obvious, and we have considered two further scenarios (Figure 1C, M2 and M3). MIIC inheriting BCs may collect more antigen from FDC (M2). In this case the inherited MIIC provides a competitive advantage regardless of the affinity of the potentially mutated receptor for interaction with TFH. Finally, the MIIC may be a signal for differentiation to PCs independent of interaction with TFH (M3). We predicted the effects of the three models on antibodies in terms of PC quality and quantity.

Asymmetric MIIC inheritance reduced the mean affinity of PCs by less than 20%. If MIIC inheritance turned off mutation then a small increase in affinity was achieved, but neither effect is significant.

In contrast, the model predicts that asymmetric antigen inheritance can have a profound impact on PC numbers. Based on simulations with comparable GC population kinetics we found that if the MIIC inheriting daughter always differentiates into a PC (Figure 1C, M3), the number of PCs derived from a GC reaction is 5-10-fold higher than in other models (Figure 1C, M1/2) where this choice is made stochastically (Figure 1D). This is because in models with stochastic choice, TFH selection events produce PCs only 10-20% of the time. In model M3, 100% of TFH selection events produce a PC. This significant increase in early PCs may be critical for control of pathogens as higher affinity antibodies are selected. That PCs would also automatically inherit antigen would also fit with recent data suggesting that PC presentation of antigen to T cells provides negative feedback on GC reactions ([16](#)). Thus, the results of Thauinat et al provide a deterministic element in BC differentiation that was previously missing and should inspire many *in silico* and *in vivo* experiments in the near future.

Figure 1:

A: Intracellular signaling upon antigen uptake and delivery to MIIC. Ab, antibody; Ag, antigen; EE, early endosome; ER, endoplasmic reticulum; MII, MHC class II; MIIC, MHC class II compartment; PM, plasma membrane; TV, transport vesicle.

B: Scheme of asymmetric MIIC (red) inheritance.

C: GC models M1-3 for the fate of MIIC retaining BCs.

D: *In silico* effect of M1-3 (C) on the number of PCs. Values are relative to the base model without asymmetric MIIC inheritance.

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