INFECTIOUS DISEASES

Game of clones: How measles remodels the B cell landscape

Duane R. Wesemann

B cell receptor sequencing sheds light on how measles cripples the immune system long after recovery from clinical disease (see related Research Articles by Petrova *et al.* and Mina *et al.*).

Measles infection does something interesting to the immune system. Beyond causing a transient lymphopenia during acute infection, the immune system remains subdued 2 to 3 years after measles viral clearance and lymphocyte recovery, leading to morbidity and mortality from secondary infections (*1*). Despite this, people generally do not get infected with measles twice. In this regard, measles induces an effective, durable anti-measles immune response. How measles infection has such a long-lasting deleterious effect on the immune system while allowing robust immunity against itself has been a burning immunological question.

In this issue of *Science Immunology*, Petrova *et al.* (*2*) offer some clues by evaluating immunoglobulin (Ig) repertoires in unvaccinated children before and after measles infection. By sampling naïve and memory B cells after the size of both pools recovered to pre-measles levels, they found that the Ig repertoires of both compartments were altered in the wake of measles (*2*). A study by Mina *et al.* (*3*) published concurrently in *Science* used the same cohort of study participants to examine antibody recognition of common viruses and found substantially diminished serological responses in post-measles samples. Mina *et al.* (*3*) convincingly showed that much of the measles-induced immune damage can be explained by the loss of long-lived plasma cells that produce secreted antibodies. Petrova *et al.* (*2*) excluded plasma cells from their analysis, focusing instead on nonsecreted Ig repertoires expressed by naive and memory B cells. Both studies offer clues to some long-standing questions regarding how measles influences the immune system and also provide fundamental insights into the flexibility and limitations of adaptive immunity. This commentary covers Petrova *et al.* (*2*) published in this issue of *Science Immunology*.

Ig repertoires are expressed on B cell surfaces as B cell receptors and can also be secreted as soluble antibodies. Whereas each B cell produces a single Ig, different B lineage cell populations produce distinct Ig repertoires. The earliest Ig repertoire generated is within progenitor (pro-) and precursor (pre-) B cells, where Ig heavy (H) and light (L) chain variable (V) region exons are assembled from gene segments. In the case of IgH, gene segments include many dozens of VH segment options, which are clustered in tandem upstream of the diversity (DH) cluster, which is, in turn, upstream of the joining (JH) cluster. The assembly process [i.e., V(D)J recombination] assembles a VH, DH, and JH to form an IgH variable region exon. The initial selection of these segments, particularly the VH segments, is not random. The IgH repertoire in pro–B cells is heavily biased because of the preferential usage of DH-proximal VH gene segments during V(D)J recombination. As B cells continue to develop into mature naïve B cells, the Ig repertoire changes substantially, largely due to tolerance filters removing autoreactive and polyreactive specificities (*4*). Upon activation, B cells can clonally expand, undergo IgH isotype class switch recombination from IgM to other IgH isotypes (i.e., IgG, IgE, and IgA), and undergo V region exon somatic hypermutation and affinity maturation. B cells can then differentiate into memory B cell pools and/or antibody-secreting plasma cell pools harboring repertoires that matured in response to prior immune experience.

Petrova *et al.* sequenced mature naïve and memory B cell compartments in blood before and then again around 40 days after the onset of measles infection (based on appearance of a skin rash). As controls, they sequenced the same B cell subsets from healthy and flu-immunized individuals after a similar time interval had elapsed. Importantly, the authors took several additional steps to ensure fair Ig repertoire comparisons. They observed that B lymphocyte counts had recovered to pre-measles levels at the time of post-measles sampling. In addition, they collected similar cell numbers and sequenced similar read depths across all samples. With these considerations, they observed that measles induced a greater change in IgH repertoire sequence features than flu vaccination in both naïve and memory B cells.

Measles directly infects lymphocytes including B and T memory cells. This contributes to memory cell loss previously proposed to result in an immune amnesia (*5*). Petrova *et al.* (*2*) provide a glimpse into what the memory Ig repertoire looks like after lymphocyte recovery. They found loss of previously expanded B memory clones, and in its place, a memory pool of increased Ig diversity. They also found more IgH class–switched isotypes with a higher level of somatic hypermutation.

The idea of memory lymphocyte depletion as a mechanism for prolonged susceptibility to infections makes sense. The Ig repertoire in memory B cells represents a system for more efficient recognition and response to prior infections. Removal of part of the memory Ig repertoire would be expected to render participants more susceptible to infections that they would otherwise have cleared more effectively with the help of memory.

In the wake of memory cell destruction and recovery, robust anti-measles immunity is established. What do the post-measles memory cell Ig repertoires look like? One might expect measles immunity to be dominant in the new memory B cell bank, perhaps with new oligoclonal expansions. However, this was not the case. Post-measles memory cells were more diverse than the pre-measles memory pool (*2*), and it is not clear what portion of the diverse post-measles memory Ig repertoire is measles specific. Although the more diverse memory repertoire could represent measles reactivity, it is also possible that the

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acute void in the memory cell compartment is filled, in part, by a diverse set of clones binding to unidentified antigens or non-native ("dark") forms of antigen (*6*). As nonspecific activation has been shown to maintain memory B cell pools (*7*), it may be that polyclonal activation of naïve mature B cells may push polyclonal diversity into the memory B cell repertoire space.

With respect to the naïve B cell pool, Petrova *et al.* (*2*) showed reduced post-measles correlation of VH-JH usage frequencies compared with pre-measles levels. A shorter CDR3H post-measles was also noted and suggested to be a marker of immaturity based on referenced studies looking at organismal ontogeny (e.g., fetal B cells have shorter CDR3s compared with postnatal B cells). However, early B lineage cells in the bone marrow have longer CDR3H lengths compared with mature naïve B cells in the context of cellular ontogeny within an individual (*8*). The CDR3H length perturbations observed post-measles may therefore not provide a robust single marker for assessing Ig repertoire maturity.

Among the measles-infected group, 2 of 19 post-measles study participants had profound changes in the mature naïve Ig repertoire characterized by heavy usage of DH-proximal VH segments, reminiscent of immature Ig repertoires usually counterselected before entering the mature naïve B cell pool. While this degree of skewing of the repertoire requires further validation given the low frequency with which it was observed in this study, it raises the question whether measles infection may have some impact on the developmental Ig filtration process in certain individuals (Fig. 1).

In contrast to the straightforward logic connecting memory cell removal to immune fragility due to immune amnesia, the impact of the presence of a more immature Ig repertoire within the mature naïve Ig repertoire is not clear. More work is required to determine if this is a causal relationship. Notwithstanding, this association raises interesting questions, such as, what is the role of the immature Ig repertoire? It is highly polyreactive (*9*), and some DH-proximal VHs are known to be autoreactive—so why have they persisted throughout evolution to be preferentially utilized in V(D)J recombination only to be heavily counterselected by developmental Ig filters? One possibility is that recapitulation theory (characterized by Ernst Haeckel's phrase "ontogeny recapitulates phylogeny") applies to B lineage repertoire development. In other words, ontogenetic B cell development could recapitulate the more innate features of more ancient life forms through phylogeny. A nonmutually exclusive alternative is that polyreactivity/autoreactivity may harbor protective utility (*10*), and its relative abundance in the immature Ig repertoire could be a storehouse of Ig repertoire innateness for demand-driven availability as recently proposed (*4*).

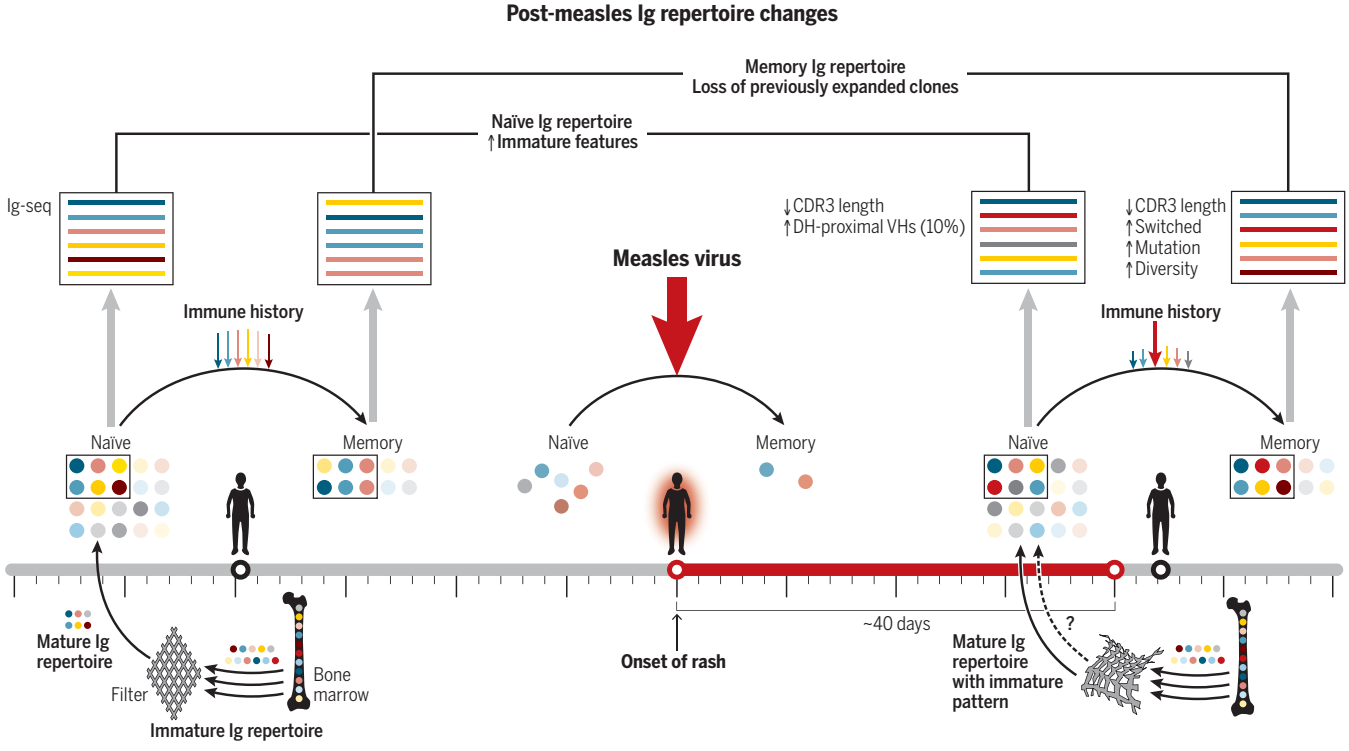

Fig. 1. Measles-induced lymphopenia results in altered naïve and memory B cell receptor repertoires after lymphocyte number recovery. Variable region exons of Ig heavy and light chains are assembled in early bone marrow–resident B lineage cells to produce a vast diversity of B cell receptor specificities (represented by multicolored bone marrow). Most of this agnostically generated immature Ig repertoire is counterselected through tolerance filtration steps (represented by a square patch of filter material), releasing a fraction of the initial immature Ig repertoire expressed on mature naïve B cells. Mature naïve B cells can be activated by infections and vaccines to undergo clonal selection, somatic Ig mutation, and IgH class switch recombination from initially expressed IgM/IgD to IgG, IgA, or IgE. After activation, some B cells specific for past infections persist as memory B cells. The memory B cell pool is a way that B cells retain memory of immune history (represented by colored arrows). Measles virus results in the destruction of immune cells, including naïve and memory B cells, leading to lymphopenia that abates weeks after infection. Ig repertoire sequencing (Ig-seq) studies by Petrova *et al.* show that both naïve Ig repertoires and memory Ig repertoires are altered. They argue that the recovered Ig repertoires retain immature Ig repertoire features. This is particularly the case for 2 of the 19 measles-infected participants (~10%), which had an Ig repertoire after measles infection with heavy usage of DH-proximal VH gene segments—a feature seen in early bone marrow B lineage cells. This may suggest a transiently weakened Ig selection filter mechanism after measles in some individuals. In addition, the recovered memory B cells after measles infection somewhat paradoxically had a more diverse Ig repertoire compared with pre-measles.

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In summary, the measles virus holds a special place in immunology. Humans are its only known natural host species, it causes an aggressive inflammatory illness with rabid contagion, and it induces a years-long immunosuppression. Yet, it paradoxically leaves robust anti-measles immunity in its wake. These features combine to make the measles vaccine to be a highly effective public health intervention. Although a proven childhood vaccine to protect humans from measles has been available for years, the studies by Petrova *et al.* and Mina *et al.* represent an opportunity to examine the measles virus against the Delphic maxim to "know thyself"—because the unique relationship measles has with the human immune system can illuminate aspects of its inner workings.

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