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Thucydides' and longer-lived plasma cells

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In this issue of *Blood*, Mei and colleagues characterize the population of CD19$^-$ plasma cells in human bone marrow and provide evidence that this plasma-cell subset substantially contributes to long-lived protection against infections and vaccination.[1]

During the Peloponnesian War, the plague killed nearly one-third of the Athenian population. In his writings, *The History of the Peloponnesian War* (~450 BC), the Greek philosopher and historian Thucydides observed that "the same man was never attacked twice—never at least fatally." This was an astute observation, and probably the first to recognize that after an individual was exposed to a pathogen, he or she could be protected from disease on subsequent exposures without suffering the effects of infection. Although he did not realize it at the time, Thucydides was describing the process by which the mammalian immune system elicits long-lived serological memory that can often persist for a lifetime.[2] In the ~2500 years since, we have learned a lot about the cellular and molecular processes underlying this phenomenon. For instance, we know that plasma cells (PCs) are largely responsible for serological memory.[2-5] PCs are generated in germinal centers (GCs) from naive precursors that are activated after exposure to T cell–dependent antigens. GC B cells undergo affinity-based selection and, depending on which and when signals are received, differentiate into plasmablasts, exit the physical structure of the GC, and start heading to the bone marrow (BM). In the BM, plasmablasts begin a new life as long-lived PCs, lodged in a survival niche, comfortably surrounded by supportive cell types that enable them to do their job: secrete copious quantities of high-affinity, antibody (Ab)-specific immunoglobulin that rapidly disarms invading pathogens before the host is aware it has been infected.[3-5] Remarkably, it has been estimated that the half-life of neutralizing Abs ranges from 10 to >10 000 years, depending on the pathogen.[2] So, if those survivors from 450 BC were alive today, they may still be immune to the plague!

Although this summary gives the impression that all is known about PC biology, this is far from reality. Indeed, many caveats exist in this simplified version of events. For instance, not all PCs home to the BM; they can remain in their tissue of origin, such as spleen, lymph nodes, tonsils, or gut.[4-7] Numerous PC subsets have been identified on the basis of their expression of different immunoglobulin isotypes and homing receptors that allow trafficking to distinct sites and endow these subsets with specific functions.[4-8] Not all PCs are long-lived: both short-lived and long-lived PCs have been identified.[3,4,8] And despite the terminology, PCs are not intrinsically long-lived: they rely on a microenvironment provided by hematopoietic and nonhematopoietic cells that produce survival factors (eg, BAFF [B cell–activating factor], APRIL [a proliferation-inducing ligand], interleukin-6) critical for their long-term persistence.[3-5,8] Lastly, our immune tissues can only support the survival of a finite number of PCs; thus, continual exposure to new pathogens generates new PCs that have to compete for limited survival niches.[8,9] In the classic setting of Darwin's survival of the fittest, only those PCs capable of maintaining access to such niches will remain for protracted periods of time, whereas "weaker" PCs will be "bumped" from survival niches and undergo apoptosis.[8,9] One inference from this is that the half-life of all immunoglobulins should be approximately similar; however, this is clearly not the case because half-lives can differ by orders of magnitude.[2]

Thus, many questions remain about the nature and dynamics of PC generation and survival. Importantly, PCs not only are the linchpin of long-lived protective immunity against pathogens and, by extension, underlie the success of vaccination, but they also contribute to human diseases such as autoimmunity (eg, systemic lupus erythematosus, rheumatoid arthritis), malignancies (eg, multiple myeloma, PC leukemia), and primary immunodeficiency in which they are not produced in sufficient quantities, rendering affected individuals susceptible to pathogen infection. For these reasons, it is necessary to elucidate the "unknowns" of PC biology.

Human PCs are typically identified by a CD38^{high}CD27^{high}CD20^{low} phenotype, with expression of other markers varying depending on the tissue harvested.[6,7] Mei and colleagues have now investigated the subset of CD19$^-$ PCs.[1] These cells were largely restricted to the BM and preferentially expressed intracellular immunoglobulin (Ig)G. In contrast, CD19$^+$ PCs are detected in blood, tonsils, and spleen, as well as in BM, and most express IgA or IgG.[1,6,7] CD19$^-$ BMPCs exhibited a unique transcriptome, with elevated expression of prosurvival genes, as well as features associated with a state of advanced maturation and

terminal differentiation. Consistent with these findings, CD19$^-$ BMPCs were nonproliferating cells with greater survival capacity than CD19$^+$ BMPCs, at least during in vitro culture. However, CD19$^-$ PCs did not appear to be simply derived from CD19$^+$ PCs in the BM, because fewer somatic mutations were detected in immunoglobulin V genes of CD19$^-$ PCs as compared to CD19$^+$ PCs, implying that these PC subsets arise at different times from different precursors during the evolution of the GC response. Remarkably, despite comparable expression of CD20 by CD19$^+$ and CD19$^-$ BMPCs, only CD19$^+$ BMPCs were reduced by therapeutic B-cell depletion with rituximab, thereby suggesting that CD19$^-$ BMPCs are less dependent on circulating mature B cells for their generation/replenishment than CD19$^+$ BMPCs. Similarly, although both antigen-specific and -nonspecific PCs were detected in peripheral blood 1 week after tetanus vaccination,[1,9] none of these cells shared the phenotypic or molecular characteristics of CD19$^-$ BMPCs, implying that they are more "embedded" in their survival niche than are CD19$^+$ BMPCs and that they are the "fitter" subset of long(er)-lived PCs. Importantly, CD19$^-$ PCs were also detected in inflamed tissues and BM of autoimmune patients and could produce autoreactive IgG.[1] Thus, although rituximab can deplete short-lived plasmablasts and improve disease in some settings of autoimmunity,[10] targeting these long-lived PCs will also be necessary for effective or improved therapeutic approaches to treating these disorders.

This study has reminded us of, and further defined, the heterogeneity and complexity that exists within what we generally consider to be the pool of human long-lived PCs.[1,7] It also provides a possible explanation for the varying serum half-lives of protective Abs, with some antigens/pathogens perhaps preferentially inducing CD19$^-$ vs CD19$^+$ PCs. Now, understanding how this could be achieved for all antigens may allow us to avoid future plagues that Thucydides so famously and accurately documented.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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Q: 1_If the possessive form is intended, what does it refer to? Do you mean "Thucydides' plasma cells and longer-lived plasma cells"? If not, is a word missing? If not, please change Thucydides' to Thucydides. Please change to "Thucydides", thanks

Q: 2_To ensure correct PubMed indexing and searchability for all authors, please highlight the surname for each author in the author group. If the surname includes multiple parts, ensure that all parts are highlighted. Done

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Q: 4_OK to change T to T cell? Yes - this is fine

Q: 5_Does edit preserve your intent?(change "they begin" to "plasmablasts begin") Yes - this is fine

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