CD19-pathogens perhaps preferentially inducing half-lives of protective Abs, with some antigens/a possible explanation for the varying serum pool of human long-lived PCs. It also provides exist within what we generally consider to be the de treating these disorders.

It could produce autoreactive IgG. Thus, although rituximab can deplete short-lived plasmablasts and improve disease in some settings of autoimmunity, 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 exist within what we generally consider to be the pool of human long-lived PCs. 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 warned of by treating these disorders.

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

REFERENCES

(Top) Heat-shock protein H1 (HSPH1) binds to client proteins (CPs) involved in lymphomagenesis (eg, c-Myc, BCL-6) to generate a “mature complex” that contributes to the stabilization and maturation of those proteins, promoting their cellular function. (Bottom) HSP inhibitors would prevent binding of CPs to HSPH1, remaining in the cytosol, where CPs are ubiquitinated (Ub) and subsequently degraded by the proteasome.
Remarkably, in c-Myc expression seen in the indolent lymphoma. was significantly increased compared with the expression seen in the indolent lymphoma. Remarkably, in c-Myc lymphomas, HSPH1 protein expression correlated with that of c-Myc.

Overall, these data suggest that HSPH1 inhibition could potentially be useful in those lymphomas with c-Myc alterations (ie, Burkitt and the so-called “double-hit” lymphomas—mature B-cell lymphomas with a translocation affecting c-Myc in combination with another translocation usually affecting bcl-2). This is of paramount relevance, in particular for the latter, amounting to a poor-prognosis lymphoma for which no effective therapies have been developed so far.

A few studies have addressed the inhibition of other HSPs as a treatment of B-cell lymphoma. In particular, HSP90, an important chaperone involved in cancer, is frequently expressed in DLBCL and, importantly, its expression highly correlates with BCL-6, a transcription factor that is frequently deregulated in DLBCL. Experimentally in vitro and in vivo studies showed that a purine-derived HSP90 inhibitor, PUIH71, selectively killed primary DLBCL-overexpressing BCL-6 and HSP90, and this approach is being translated into the clinical scenario in patients with lymphoma with the new available HSP90 inhibitors. Although early trials with HSP inhibitors in lymphoma patients have not shown impressive clinical activity, it may be envisioned that a combination of different HSP inhibitors targeting distinct oncogenic proteins may improve their efficacy and may add value to conventional immunotherapy.

Pharmacologic inhibitors of HSPH1 have yet to be developed, but the discovery of HSPH1 as a chaperone of c-Myc in B-cell lymphoma presents an important opportunity to design rational, molecularly based treatments for c-Myc–dependent B-cell lymphomas such as Burkitt lymphoma and the “double-hit” DLBCL.

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

**REFERENCES**


Heat-shock proteins: a c-Myc lymphoma target?

Javier Briones