Problematic Host Cell Proteins - Clusterin

Biochimica et Biophysica Acta, 1159 (1992) 319–326

BBAPRO 34308

Clusterin binds by a multivalent mechanism to the Fc and Fab regions of IgG

Mark R. Wilson and Simon B. Easterbrook-Smith

Department of Biochemistry, University of Sydney, Sydney (Australia)

(Received 9 April 1992)

When doing Host Cell Protein analysis by mass spectrometry, we often fail to appreciate the "why" of the HCPs that show up in our protein lists – *why* did these HCPs co-purify with the Product, and *why* are they important? Clusterin shows up in almost every HCP project we work on. *Why?*

If we look in UniProt, we see this annotation of clusterin function:

- *Functions as extracellular chaperone that prevents aggregation of non-native proteins.*
- *Prevents stress-induced aggregation of blood plasma proteins*.

However, if we go back almost 20 years in the literature to 1992, we find an article by Wilson and Easterbrook-Smith that provides results from simple but elegant experiments that reveal additional important properties of clusterin, especially with respect to the host cell protein field:

1. Clusterin binds with high affinity to both Fc *and* Fab domains of IgG
2. Clusterin binding to IgG shows positive cooperativity. The authors speculate clusterin's natural tendency to aggregate is the cause.
3. Clusterin binds human immunoglobulins with an affinity ordering of $IgG_3 > IgG_4 > IgM > IgG_1 > IgG_2 > IgA$
4. The binding of clusterin with IgG is strong enough that clusterin can be used to affinity purify IgG from plasma
5. Finally, Protein A does not compete with clusterin for binding to the Fc region of IgG

These results provide us with insights as to why clusterin is such a problem HCP, especially with mAbs and Fc-fusion proteins. These results also provide potential clues as to why MS results often give much higher HCP numbers than ELISA when clusterin is a prominent HCP. "Old" articles like this can shed light on why it is important to use new technologies like mass spectrometry to detect and quantify problematic HCPs like clusterin in your products.