Why does serum contain ferritin?

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In a recent article, Koperdanova and Cullis \(^1\) rehearsed the various interpretations of raised serum ferritin levels. In fact the most interesting question \(^2\) is why does ferritin appear in serum at all?

All modern network models of iron metabolism (e.g. \(^3\)\(^-\)\(^7\)) have iron being passed from the gut to peripheral cells via blood (serum) bound to transferrin, a well-established iron-transporting molecule that is present in serum at ca 0.6-3.3 g.L\(^{-1}\) \(^8\). By contrast, ferritin is an intracellular iron storage compound \(^3\)\(^5\)\(^7\); its normal range for serum is at levels 10,000-100,000 times lower than that for transferrin, being from very small levels to up to 300 µg.L\(^{-1}\) in men and slightly lower in women \(^2\).

While it was once thought that serum ferritin levels might reflect liver iron stores, our modern understanding (and the systems biology models) recognise, as indeed do Koperdanova and Cullis \(^1\), that it is far more commonly an inflammatory marker. All the evidence, however, it that it appears in serum by dint simply of cell death, and is thereby a cell death marker \(^2\).

Normally, serum ferritin is assessed via an antibody test, that detects only the protein. Where measurements to measure its iron content as well \(^9\)\(^-\)\(^11\), the serum ferritin itself is found to have lost almost all its iron \(^2\). The free iron thereby liberated can prove cytotoxic, both by catalysing the Fenton reaction to produce hydroxyl radicals \(^4\)\(^12\)\(^-\)\(^14\), and by the awakening of dormant microbes whose lipopolysaccharide can produce the inflammation characteristic of such diseases \(^15\)\(^-\)\(^17\).

We think that it is time for a re-evaluation of what serum ferritin measurements are really telling us.

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