Title:	Calcium Binding to Beta-2-Microglobulin at Physiological Ph Drives the Occurrence of Conformational Changes Which Cause the Protein to Precipitate into Amorphous Forms That Subsequently Transform into Amyloid Aggregates
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Abstract:	Using spectroscopic, calorimetric and microscopic methods, we demonstrate that calcium binds to beta-2-microglobulin (β2m) under physiological conditions of pH and ionic strength, in biological buffers, causing a conformational change associated with the binding of up to four calcium atoms per β2m molecule, with a marked transformation of some random coil structure into beta sheet structure, and culminating in the aggregation of the protein at physiological (serum) concentrations of calcium and β2m. We draw attention to the fact that the sequence of β2m contains several potential calcium-binding motifs of the DXD and DXDXD (or DXEXD) varieties. We establish (a) that the microscopic aggregation seen at physiological concentrations of β2m and calcium turns into actual turbidity and visible precipitation at higher concentrations of protein and β2m, (b) that this initial aggregation/precipitation leads to the formation of amorphous aggregates, (c) that the formation of the amorphous aggregates can be partially reversed through the addition of the divalent ion chelating agent, EDTA, and (d) that upon incubation for a few weeks, the amorphous aggregates appear to support the formation of amyloid aggregates that bind to the dye, thioflavin T (ThT), resulting in increase in the dye's fluorescence. We speculate that β2m exists in the form of microscopic aggregates in vivo and that these don't progress to form larger amyloid aggregates because protein concentrations remain low under normal conditions of kidney function and β2m degradation. However, when kidney function is compromised and especially when dialysis is performed, β2m concentrations probably transiently rise to yield large aggregates that deposit in bone joints and transform into amyloids during dialysis related amyloidosis.
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