Apoptin induces tumor-specific apoptosis as a globular multimer

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The chicken anemia virus-derived Apoptin protein induces tumor-specific apoptosis. Here, we show that recombinant Apoptin protein spontaneously forms noncovalent globular aggregates comprising 30 to 40 subunits in vitro. This multimerization is robust and virtually irreversible, and the globular aggregates are also stable in cell extracts, suggesting that they remain intact within the cell. Furthermore, studies of Apoptin expressed in living cells confirm that Apoptin indeed exists in large complexes in vivo. We map the structural motifs responsible for multimerization in vitro and aggregation in vivo to the N-terminal half of the protein. Moreover, we show that covalently fixing the Apoptin monomers within the recombinant protein multimer by internal cross-linking does not affect the biological activity of Apoptin, as these fixed aggregates exhibit similar tumor-specific localization and apoptosis-inducing properties as non-cross-linked Apoptin. Taken together, our results imply that recombinant Apoptin protein is a multimer when inducing apoptosis, and we propose that this multimeric state is an essential feature of its ability to do so. Finally, we determine that Apoptin adopts little, if any, regular secondary structure within the aggregates. This surprising result would classify Apoptin as the first protein for which, rather than the formation of a well defined tertiary and quaternary structure, semi-random aggregation is sufficient for activity.
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