Title:	Insufficient (sub-native) helix content in soluble/solid aggregates of recombinant and engineered forms of IL-2 throws light on how aggregated IL-2 is biologically active
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Abstract:	Interleukin 2 (IL-2) is an extremely aggregation-prone, all-alpha helical cytokine. In its receptor-bound state, ~72 % of the polypeptide chain adopts helical structure and there is no beta sheet content whatsoever. In the past, recombinant IL-2 has been formulated and used therapeutically in humans, following production in E. coli. Therapeutic IL-2 consists entirely of functionally-active soluble aggregates with ~30 subunits per aggregate particle. Side-effects attributed to aggregation resulted in discontinuation of usage over a decade ago. Structurally, and biochemically, activity in IL-2 aggregates can potentially be explained in one of two ways: (a) individual IL-2 chains exist in sterically-accessible, receptor binding-competent (native) structures, allowing aggregates to bind directly to IL-2 receptors (IL-2R); alternatively, (b) IL-2 chains dissociate from aggregates, become free to adopt native structure, and then bind to IL-2R. We produced native IL-2 and numerous engineered forms in E. coli with the objective of obtaining insights into these possibilities. Each IL-2 variant was subjected to size exclusion chromatography, circular dichroism (CD) and Fourier transform infrared spectroscopy (FTIR). All forms produced and studied (including those with native IL-2 sequences) turned out to aggregate and also display less than ~50 % helix content as well as significant beta sheet content. No conditions were found that obviate aggregation. Aggregated IL-2 is thus insufficiently native-like to bind to IL-2R. Activity in aggregates thus probably owes to adoption of receptor binding-competent structures by chains that have already dissociated from aggregates.
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