Title:	Probing protease sensitivity of recombinant human erythropoietin reveals α3-α4 inter-helical loop as a stability determinant
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Keywords:	Cathepsin L Circulating half-life in vivo clearance Inter-helical loop region
Issue Date:	2015
Publisher:	John Wiley and Sons Inc.
Citation:	Proteins: Structure, Function and Bioinformatics, 83(10) pp. 1813-1822.
Abstract:	Although unglycosylated HuEpo is fully functional, it has very short serum half-life. However, the mechanism of in vivo clearance of human Epo (HuEpo) remains largely unknown. In this study, the relative importance of protease-sensitive sites of recombinant HuEpo (rHuEpo) has been investigated by analysis of structural data coupled with in vivo half-life measurements. Our results identify α3-α4 inter-helical loop region as a target site of lysosomal protease Cathepsin L. Consistent with previously-reported lysosomal degradation of HuEpo, these results for the first time identify cleavage sites of rHuEpo by specific lysosomal proteases. Furthermore, in agreement with the lowered exposure of the peptide backbone around the cleavage site, remarkably substitutions of residues with bulkier amino acids result in significantly improved in vivo stability. Together, these results have implications for the mechanism of in vivo clearance of the protein in humans
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