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Changing the net charge from negative to positive makes ribonuclease Sa cytotoxic

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Abstract

Ribonuclease Sa (pI = 3.5) from *Streptomyces aureofaciens* and its 3K (D1K, D17K, E41K) (pI = 6.4) and 5K (3K + D25K, E74K) (pI = 10.2) mutants were tested for cytotoxicity. The 5K mutant was cytotoxic to normal and v-ras-transformed NIH3T3 mouse fibroblasts, but RNase Sa and 3K were not. The structure, stability, and activity of the three proteins are comparable, but the net charge at pH 7 increases from -7 for RNase Sa to -1 for 3K and to +3 for 5K. These results suggest that a net positive charge is a key determinant of ribonuclease cytotoxicity. The cytotoxic 5K mutant preferentially attacks v-ras-NIH3T3 fibroblasts, suggesting that mammalian cells expressing the ras-oncogene are potential targets for ribonuclease-based drugs.

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Keywords

Charge reversal mutants, Cytotoxicity, Net charge, Ribonuclease Sa, v-ras-transformed fibroblasts