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A hydrophobic segment of some cytotoxic ribonucleases

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ABSTRACT

The exact mechanism by which cytotoxic ribonucleases reach the cytosol of tumor cells remains unclear. The interaction of ribonucleases with a lipid bilayer is involved in the translocation of ribonucleases across the endosomal membrane. Here, we aimed to study the hydropathy character of toxic antitumor ribonucleases (bovine seminal ribonuclease and binase) and two non-toxic ribonucleases (bovine pancreatic ribonuclease and human pancreatic ribonuclease) by sliding-window hydrophobicity analysis. Comparative hydropathy plot analysis of the non-toxic pancreatic ribonucleases and their toxic variants was also performed. The data obtained indicate that some cytotoxic ribonucleases have a hydrophobic segment, which is sterically available for the hydrophobic interaction with a tumor cell membrane and endosomal membrane. After dissociation, subunits of dimeric ribonucleases are probably capable of thermodynamically favorable interaction with the interfacial region of a lipid bilayer. Remarkably the hydrophobic segment is not identified in the amino acid sequences of non-toxic ribonucleases. The paper describes the hydrophobic properties of toxic RNases that are essential for both the model of a lipid–protein interaction and the cytotoxicity mechanism unraveling.

Introduction

The cytotoxic ribonucleases (RNases) are found among members of both RNase A superfamily and RNase T_1 family RNases. Over the past decade there has been increasing research in the RNase functions related to the gene expression control, cell growth and differentiation, cell protection from pathogens, and apoptosis induction. RNases with special biological actions include bovine seminal RNase (BS-RNase) and RNase from *Bacillus intermedius* 7P (binase), both endowed with a strong antitumor effect [1–3]. Details of the mechanism of RNase antitumor action remain unclear. Comprehensive study of the RNases structure is of great importance for unraveling the cytotoxicity mechanisms. Although the number of resolved RNase three-dimensional structures rapidly increases, little has been published on the structural key of the cytotoxicity.

It has been established by recent studies that cationization is a powerful strategy to promote antitumor effects of RNases [4,5]. This approach allows one to decrypt the role of cationic amino acid residues in adsorption of toxic RNases on a cytoplasmic membrane of malignant cells, because some of them express more acid phospholipids in the membrane outer leaflet than their non-malignant counterparts [6,7]. However, cationic properties may not be the only reason for RNase cytotoxicity [8].

Intensive study of electrostatic properties with regard to RNases toxicity contributed to disclosure of the mechanisms of RNase-tumor cell surface interaction. Logically, the first stage of the interaction appears to be adsorption on a cell surface. Consequently, the selective antitumor action of cationic RNases may be explained through electrostatic interaction. Subsequently, RNases undergo cytosolic internalization via dynamin-independent endocytic pathway [9]. This implies that RNases are subject to translocation through the endosome membrane, meaning that protein molecules interact with the hydrophobic region of a lipid bilayer. The hydrophobic properties of RNases, which provide a thermodynamic prerequisite for the translocation, deserve further investigation.

A number of algorithms have been proposed to identify the hydrophobic (HΦ) α-helical segments [10–12]. The main idea behind our approach is a sliding-window hydrophobicity analysis of amino acid sequences, and a helical wheel approach combining with a molecular modeling. An *in silico* algorithm based on Wimley–White scale was used [13,14]. The latter numerically ranks each amino acid residue with a thermodynamic parameter reflecting the likelihood of finding that residue in a HΦ segment.

Subjects of the research were BS-RNase, binase, bovine pancreatic RNase A (BP-RNase), and human pancreatic RNase A (HP-RNase). The aim of the paper is to determine the hydropathic character of non-toxic and toxic RNases. The structures of

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