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Introduction: the ribonuclease A superfamily

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Abstract. In this multi-author issue several aspects of the ribonuclease A superfamily are reviewed. This superfamily can be subdivided in a number of mammalian and other vertebrate ribonuclease families. In the introduction chapter the titles of the other contributions are presented. There is little uniformity in the nomenclature of ribonucleases, caused in part by gene duplications, which have occurred independently in several mammalian lineages, and which are nice examples for explaining orthology and paralogy in molecular evolution.

Key words. Orthology; paralogy; ribonuclease A.

The publication of the book *Ribonucleases: Structures and Functions* (edited by G. D'Alessio and J. F. Riordan; Academic Press) with 19 very interesting reviews on this subject highlighted the beginning of the year 1997. This review volume presents a well-balanced, timely overview of the field of current ribonuclease research. However, developments in this field happen fast, and in the last 2 years several novel observations and discoveries have been made. Therefore, another review on ribonucleases will not be just a repetition of the previous one. In this multi-author review only proteins, homologous with the 'old faithful' bovine pancreatic ribonuclease A will be discussed, and somewhat more emphasis will be given to several comparative aspects than in previous reviews.

The Introductory chapter of the ribonucleases book [1] as well as two earlier papers published by Benner and Allemann [2] and D'Alessio [3] note that, after serving duty for Noble prize-winning research, by 1980 ribonuclease was considered to be a dull enzyme, without even a digestive function in humans. Since then the enzyme has enjoyed a renaissance through the discovery of proteins with novel biological actions, which after structural studies proved to be homologous with ribonucleases. Their ribonuclease activity was found to be a condition of these special actions. How gratifying for us that when in the mid-1980s the primary structures of two 'of the few remaining' ribonucleases were determined by classical protein sequencing and shown to deviate substantially from those of others, that one of them – turtle pancreatic ribonuclease [4] – turned out to share more structural features with human angiogenin [5] than with mammalian ribonucleases, while the other – a novel ribonuclease isolated from human urine [6] – was identical to eosinophil-derived neurotoxin (EDN) [7, 8].

This multi-author review starts with a discussion by Nogués et al. [9] on several substrate-binding features of bovine pancreatic ribonuclease A, followed by a summary of structures and properties of four frog ribonucleases by Irie et al. [10]. Next are papers on human ribonucleases by Sorrentino [11], eosinophil ribonucleases 2/3 by Rosenberg [12], ribonucleases 4 by Hofsteenge et al. [13] and the angiogenins by Strydom [14]. In a final concluding article we summarize several studies on mammalian ribonucleases 1 and present a general discussion on the ribonuclease A superfamily [15].

As will already be clear from the previous paragraph, there is not much uniformity in the nomenclature of ribonucleases. Ribonucleases homologous with bovine pancreatic ribonuclease A have been found so far only

Table 1. Nomenclature of mammalian members of ribonuclease A superfamily.

			Human [18, 12]	Ox [20, 16, 14]	Mouse [12, 14]
Secretory [17] (plasma/pancreas type)	pt [11]	pancreatic-type [16]	RNase 1 (HPR [19])	RNase A (pancreas) BS RNase, RNase S (semen) BRb RNase, RNase B (brain)	RNase 1, mPr [12]
Nonsecretory [17] (liver/spleen type)	npt [11]	neurotoxin-type [16]	RNase 2 (EDN; HLRNase [19]) RNase 3 (ECP [12])		mEAR-1 mEAR-2 mR-3 mR-4 mR-5 mR-6P
			RNase 6 (hRK6 [12])	RNase K2 (bRK6) [12]	
	pt/npt [11]	liver-type [16]	RNase 4	RNase BL4 [19]	
Angiogenin	ang [11]		RNase 5	Ang-1 Ang-2	Ang-1 Ang-3 Ang-4 Ang-2 (AngRP) Ang-ps1 Ang-ps2

in mammals, birds, reptiles and amphibians [16]. These ribonucleases may be considered to be members of the superfamily of ribonucleases A, to indicate the homology with bovine ribonuclease A. This name provides a suitable distinction from two other well-investigated superfamilies of the T_1 and the T_2 ribonucleases, which are not homologous with ribonucleases A. Of course, it should be kept in mind that here the letter 'A' has a different meaning than that originally proposed for the bovine pancreatic enzyme, and it no longer refers to a particular glycosylation state. The superfamily of ribonucleases A can be subdivided into a number of mammalian and other vertebrate ribonuclease families with an often confusing nomenclature. Table 1 lists names used in four mammalian families, with examples of enzymes from humans, mouse and ox as representatives of the most intensively investigated species, for which we also may expect more extensive information from total genomic sequence studies in a not-too-distant future.

Mammalian members of the ribonuclease A superfamily provide a nice opportunity to explain special examples of orthology and paralogy in molecular evolution [21]. Orthology indicates common ancestry by species divergence and paralogy by gene duplication. However, if gene duplications have occurred after species divergences, one should be careful in defining orthology and paralogy. Human ribonucleases 2 and 3 are the product of a gene duplication which occurred in an ancestor of Old World monkeys and apes after their divergence from the ancestor of New World monkeys [12]. This means that by definition there are no separate ribonucleases 2 and 3 in other primates or other mammals. Likewise, pancreatic, seminal-type and brain-type ribonucleases in ruminants are the product of gene duplications which occurred in ancestral ruminants [20]. This also means, for instance, that an orthologue of an enzyme like bovine seminal ribonuclease (BS RNase) does not occur outside this taxon. Bovine pancreatic, seminal and brain ribonucleases are paralogous proteins, but are orthologues of ribonucleases 1 (pt RNases) in other mammalian orders.

We hope that not only the separate articles in the multi-author review, but also their variety, will give interested readers a comprehensive insight into current research on members of the ribonuclease A superfamily.

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