

# Subsystem: Ribonucleotide Reduction

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Ribonucleotide reductases (RNRs) catalyse the reduction of ribonucleotides to their corresponding 2'-deoxyribonucleotides and therefore play an essential role in DNA synthesis [1]. There are three classes of RNR with different primary structures, subunits, cofactor requirements, and regulation, but all of them are allosterically regulated [2].

Class I RNRs are aerobic enzymes composed of two homodimeric proteins, which are widely distributed both in prokaryotes and eukaryotes. Class I is divided into two distantly related subclasses, NrdAB (Ia) and NrdEF (Ib), which are similar on the sequence level but form distinct branches on the phylogenetic trees.

Single-subunit class II RNRs, named NrdJ, require coenzyme-B12, or S-adenosylcobalamine as a radical generator and do not depend on oxygen. Occurring in deeply rooted eubacteria, archaea and bacteriophages, NrdJ proteins are distantly related to NrdA and NrdE [3].

Members of class III RNRs are expressed in strict anaerobes and in certain facultative anaerobes during growth under anaerobic conditions (in *E. coli* *nrdDG* is regulated by a regulator of anaerobiosis, FNR). The large catalytic subunit of class III RNR, encoded by *nrdD* gene, is not related to Class I and Class II RNRs. NrdD is in its active form a homodimer. The smaller subunit NrdG is an iron sulfur protein, also known as NrdD-activating protein, that catalyzes the one-electron transfer from reduced flavodoxin to S-adenosylmethionine to generate a stable glycine radical near the carboxy-terminal portion of the NrdD subunit.

The *Escherichia coli* genome contains three RNRs operons, *nrdAB*, *nrdHIEF* and *nrdDG*.

NrdR is a novel transcriptional regulator of all RNRs, which was predicted using comparative genomics analysis of regulation of ribonucleotide reductase genes in bacterial genomes. A highly conserved palindromic signal with consensus sequence acaCwAtATaTwGtg, named NrdR-box, was identified upstream of most operons encoding ribonucleotide reductases of three different classes. By correlating the occurrence of NrdR-boxes with phylogenetic distribution of ortholog families we were able to identify a transcriptional regulator containing Zn-ribbon and ATP-cone motifs (COG1327) for the predicted ribonucleotide reductase regulon [5].

## References.

1. Reichard P. From RNA to DNA, why so many ribonucleotide reductases? *Science*. 1993; 260:1773-7.
2. Torrents E, et al. Ribonucleotide reductases: divergent evolution of an ancient enzyme. *J Mol Evol*. 2002; 55:138-52.
3. Jordan A, et al. B12-dependent ribonucleotide reductases from deeply rooted eubacteria are structurally related to the aerobic enzyme from *Escherichia coli*. *Proc Natl Acad Sci U S A*. 1997; 94:13487-92.
4. Torrents E, et al. Occurrence of multiple ribonucleotide reductase classes in  $\gamma$ -proteobacteria species. *Curr Microbiol*. 2000; 41:346-51.
5. Rodionov DA, and Gelfand MS. Identification of a Bacterial Regulatory System for Ribonucleotide Reductase by Phylogenetic Profiling. *Trends in Genetics*, 2005; 7.

**Fig. 2. Ribonucleotide reduction. Subsystem spreadsheet.**

Organism	Variant Code	RNR Class Ia		RNR Class Ib			RNR Class II	RNR Class III		Regulator
		RNR1a_A	RNR1a_B	RNR1b_A	RNR1b_B	NrdI	RNRII	RNRIII	RNRIII_AP	RNRTR
<i>Neisseria meningitidis ser. C</i>	1	<a href="#">273</a>	<a href="#">271</a>							<a href="#">1193</a>
<i>Aquifex aeolicus VF5</i>	1	<a href="#">77</a>	<a href="#">1055</a>							
<i>Rubrobacter xylophilus DSM 9941</i>	2						<a href="#">2363</a>			<a href="#">2362</a>
<i>Methanococcus maripaludis S2 [A]</i>	3							<a href="#">227</a>	<a href="#">580</a>	
<i>Mycoplasma pneumoniae M129</i>	4			<a href="#">324</a>	<a href="#">322</a>	<a href="#">323</a>				
<i>Streptomyces coelicolor A3</i>	12	<a href="#">5181</a>	<a href="#">5180</a>				<a href="#">5754</a>			<a href="#">5753</a>
<i>Clostridium acetobutylicum ATCC 824</i>	123	<a href="#">3400</a>	<a href="#">3399</a>				<a href="#">1212</a>	<a href="#">1370, 649</a>	<a href="#">650</a>	<a href="#">1853</a>
<i>Haemophilus ducreyi 3500HP</i>	13	<a href="#">1463</a>	<a href="#">1464</a>					<a href="#">337</a>	<a href="#">338</a>	<a href="#">1163</a>
<i>Escherichia coli K12</i>	134	<a href="#">2207</a>	<a href="#">2208</a>	<a href="#">2636</a>	<a href="#">2637</a>	<a href="#">2635</a>		<a href="#">4148</a>	<a href="#">4147</a>	<a href="#">410</a>
<i>Pyrococcus furiosus DSM 3638 [A]</i>	23						<a href="#">452</a>	<a href="#">2023</a>	<a href="#">2024</a>	
<i>Deinococcus radiodurans R1</i>	24			<a href="#">110</a>	<a href="#">111</a>	<a href="#">109</a>	<a href="#">2554</a>			<a href="#">272</a>
<i>Bacillus cereus ATCC 10987</i>	34			<a href="#">1463</a>	<a href="#">1464</a>	<a href="#">1462</a>		<a href="#">3591</a>	<a href="#">3590</a>	<a href="#">4676</a>

**Functional variants of Ribonucleotide Reductases (RNRs):**

1. RNR of class Ia (aerobic), Alpha and Beta subunits (NrdA and NrdB) (EC 1.17.4.1)
2. RNR of class II (coenzyme B12-dependent) (NrdJ) (EC 1.17.4.1)
3. RNR of class III (anaerobic). Catalytic subunit (NrdD) (EC 1.17.4.2) and activating protein (NrdG) (EC 1.97.1.4)
4. RNR of class Ib (aerobic), Alpha and Beta subunits (NrdE and NrdF) (EC 1.17.4.1), and auxiliary protein NrdI.

The presence of a transcriptional regulator of all RNR genes (NrdR) is optional. In general, it is present in almost all bacterial species and absent in Archaea and Eukaryota.

Functional variants #12, 123, 13, 134, 23, 24, and 34 are combinations of the four basic RNR types.