Title: Another piece of the jigsaw: a new signaling axis defined by shape-specific RNR-α hexamers

Abstract: Exquisite 'checks and balances' must be in place to maintain metazoan genome stability. Endowed with the unique and essential function of converting ribonucleotides to deoxyribonucleotides (the fundamental building blocks for DNA), the enzyme ribonucleotide reductase (RNR) has arguably been the central player in genome surveillance and maintenance since the beginning of DNA-based life. The fundamental importance of this biochemical function and the complexity of RNR biochemistry have meant many other aspects of RNR function and regulation have been largely overlooked. In search of new functions of this ancient enzyme, we undertook a large-scale profiling for novel interacting proteins specific to a specific subunit of RNR (RNR-α) and discovered a novel nuclear-specific binding partner. Our further studies reveal that changes in the quaternary state of RNR-α in response to cellular nucleotide-pool imbalance are novel cues that signal for regulation of RNR-α's compartmentalization and subsequent interaction with this newly-discovered binder in the nucleus, that ultimately lead to downregulation of DNA replication. Intriguingly, this newly-identified signaling pathway also responds to a specific class of anti-lymphoma drugs in clinical use. The mechanistic advances we establish herein unveil a previously-unappreciated anti-proliferative signaling response of fundamental importance in genome protection.

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