2 Pirin is an iron-dependent redox regulator of NF-κB.

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Interesting Hypothesis, New Finding

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This paper uses biochemical and structural analysis to probe the role of the non-heme iron in mammalian pirin protein, a binding partner for the important regulator nuclear factor (NF)κB. In contrast to iron-containing bacterial proteins that bind DNA directly (e.g. SoxR and PerR), pirin acts indirectly through its association with NFκB. Reversible conversion between Fe(II) and Fe(III) in pirin generates a shape change that the authors propose is transmitted to NFκB, and they demonstrate that the DNA binding in vitro is affected dramatically. It remains to be seen whether the same redox regulation occurs in cells.

Disclosures
None declared

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No comments yet.

Comments:

Abstract:

Pirin is a nuclear nonheme Fe protein of unknown function present in all human tissues. Here we describe that pirin may act as a redox sensor for the nuclear factor κB (NF-κB) transcription factor, a critical mediator of intracellular signaling that has been linked to cellular responses to proinflammatory signals and controls the expression of a vast array of genes involved in immune and stress responses. Pirin's regulatory effect was tested with several metals and at different oxidations states, and our spectroscopic results show that only the ferric form of pirin substantially facilitates binding of NF-κB proteins to target κB genes, a finding that suggests that pirin performs a redox-sensing role in NF-κB regulation. The molecular mechanism of such a metal identity- and redox state-dependent regulation is revealed by our structural studies of pirin. The ferrous and ferric pirin proteins differ only by one electron, yet they have distinct conformations. The Fe center is shown to play an allosteric role on an R-shaped surface area that has two distinct conformations based on the identity and the formal redox state of the metal. We show that the R-shaped area composes the interface for pirin-NF-κB binding that is responsible for modulation of NF-κB's DNA-binding properties. The nonheme Fe protein pirin is proposed to serve as a reversible functional switch that enables NF-κB to respond to changes in the redox levels of the cell nucleus.

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