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Structural Biology

Molecular mechanism of specific DNA sequence recognition by NRF1

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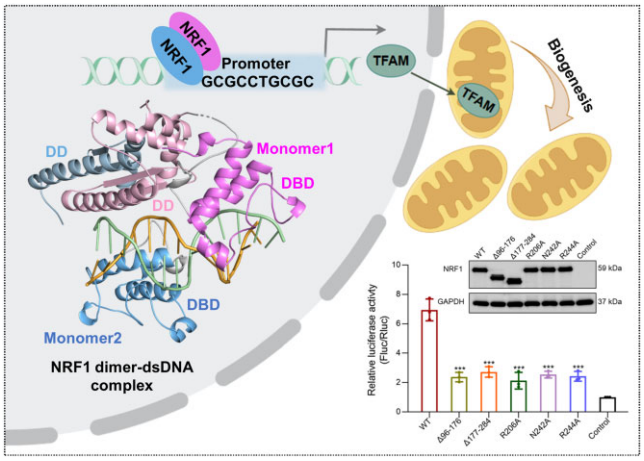
Abstract

Nuclear respiratory factor 1 (NRF1) regulates the expression of genes that are vital for mitochondrial biogenesis, respiration, and various other cellular processes. While NRF1 has been reported to bind specifically to GC-rich promoters as a homodimer, the precise molecular mechanism governing its recognition of target gene promoters has remained elusive. To unravel the recognition mechanism, we have determined the crystal structure of the NRF1 homodimer bound to an ATGCGCATGCGCAT dsDNA. In this complex, NRF1 utilizes a flexible linker to connect its dimerization domain (DD) and DNA binding domain (DBD). This configuration allows one NRF1 monomer to adopt a U-turn conformation, facilitating the homodimer to specifically bind to the two TGCGC motifs in the GCGCATGCGC consensus sequence from opposite directions. Strikingly, while the NRF1 DBD alone could also bind to the half-site (TGCGC) DNA of the consensus sequence, the cooperativity between DD and DBD is essential for the binding of the intact GCGCATGCGC sequence and the transcriptional activity of NRF1. Taken together, our results elucidate the molecular mechanism by which NRF1 recognizes specific DNA sequences in the promoters to regulate gene expression.

Graphical abstract



Introduction

Mitochondria, as essential organelles, play a vital role in supplying cellular energy. Their functions and biogenesis depend on proteins not only encoded by the mitochondrial genome but also by many nuclear genes. These nuclear gene products are indispensable for various crucial processes in the mitochondria, such as transcription, translation, and replication of mitochondrial DNA (mtDNA), mitochondrial respiration and the import of other proteins into the mitochondria (1). Among these nuclear gene products, Nuclear Respiratory Factor 1 (NRF1) and NRF2 are central to maintaining the overall functionality and biogenesis of mitochondria. They have been directly linked to the expression of genes involved in mitochondrial respiration, mtDNA transcription and replication, and mitochondrial protein import (1,2). Thus, NRF1 and NRF2 ensure efficient energy production and cellular function in mitochondria.

NRF1 was initially identified as a transcription activator of cytochrome c by binding to the cytochrome c promoter as a homodimer (3–5). Subsequently, a consensus sequence GCGCNTGCGC (N represents any nucleotide) was identified as the DNA binding motif of NRF1 (6), which has also been detected in the promoters of many other nuclear genes relevant to mitochondrial biogenesis and respiration, such as

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