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Isoform-specific variation in the intrinsic disorder of the ecdysteroid receptor N-terminal domain.

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Streszczenie

The Drosophila melanogaster ecdysteroid receptor (EcR) is a member of the nuclear hormone receptor superfamily. EcR controls animal development and metamorphosis by activating or repressing the transcription of target genes. There are three EcR isoforms, EcRA, EcRB1, and EcRB2 that exhibit diverse spatial and temporal distributions within various tissues and reveal essential functional differences. These differences can be attributed to the isoform-specific N-terminal domains (NTDs), which differ in length and primary structure. To lay a foundation for understanding of the molecular mechanism underlying functional diversity of the isoforms, we have carried out a comprehensive biochemical and biophysical analysis of purified hexahistidine-tagged EcRA and EcRB1 NTDs (EcRA-NTD and EcRB1-NTD). The results, along with in silico examinations of the primary structures indicate that the EcR NTDs exhibit properties of premolten globule-like intrinsically disordered proteins. Furthermore, we demonstrate for the first time that NTDs of isoforms of a particular nuclear hormone receptor exhibit distinct structural properties. In silico analysis revealed that the EcRA-NTD sequence has a bigger tendency for disorder than the EcRB1-NTD sequence. Accordingly, the circular dichroism experiments demonstrated that EcRA-NTD has lower regular secondary structure content than EcRB1-NTD and the size-exclusion chromatography showed that EcRA-NTD is less compact than EcRB1-NTD. Furthermore, the limited proteolysis analysis revealed that the C-terminal region common to both NTDs is more susceptible to the enzymatic cleavage in EcRA-NTD than in EcRB1-NTD. We postulate that unique conformational states of EcRA-NTD and EcRB1-NTD might act as the starting points for the functional diversity of EcRA and EcRB1 isoforms.

Słowa kluczowe

Drosophila melanogaster, ecdysteroid recep-tor, intrinsically disordered protein, N-terminal domain, nuclear hormone receptor, premolten globule

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