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Review

Emerging roles of DNA-PK besides DNA repair

Xianming Kong [a], Ying Shen [b], Na Jiang [a], Xin Fei [a], Jun Mi [b,*]

[a] Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[b] Key Laboratory of Cell Differentiation and Apoptosis of Chinese Ministry of Education, Institute of Medical Science, Shanghai Jiao-Tong University School of Medicine, Shanghai, China

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ABSTRACT

The DNA-dependent protein kinase (DNA-PK) is a DNA-activated serine/threonine protein kinase, and abundantly expressed in almost all mammalian cells. The roles of DNA-PK in DNA-damage repair pathways, including non-homologous end-joining (NHEJ) repair and homologous recombinant (HR) repair, have been studied intensively. However, the high levels of DNA-PK in human cells are somewhat paradoxical in that it does not impart any increased ability to repair DNA damage. If DNA-PK essentially exceeds the demand for DNA damage repair, why do human cells universally express such high levels of this huge complex? DNA-PK has been recently reported to be involved in metabolic gene regulation in response to feeding/insulin stimulation; our studies have also suggested a role of DNA-PK in the regulation of the homeostasis of cell proliferation. These novel findings expand our horizons about the importance of DNA-PK.

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1. Introduction

The DNA-dependent protein kinase (DNA-PK) is a DNA-activated serine/threonine protein kinase, and abundantly expressed in almost all mammalian cells. DNA-PK has been mainly known as a critical component in the DNA-damage repair pathway, including non-homologous end-joining (NHEJ) repair and homologous recombinant repair. Homozygous knock-out mice of DNA-Pk catalytic subunit (DNA-PKcs$^{-/-}$) are hypersensitive to radiation and chemical treatment, and have defects in V(D)J recombination. Although DNA-PK is highly expressed in human cells, the other NHEJ factors are not as abundant. The high levels of DNA-PK in human cells are also somewhat paradoxical in that it does not impart any increased ability to repair DNA damage. If the amount of expressed DNA-PK essentially exceeds the demand for DNA-damage repair, why do human cells universally express such high levels of this huge complex?

The data from the Sur lab have showed DNA-PK is involved in metabolic gene regulation in response to insulin. DNA-PK regulates fatty acid synthesis by modulating the protein expression of fatty acid synthase (FAS) in a feeding-dependent manner. DNA-PK induces the activation of Upstream Stimulatory Factor 1 (USF-1), which sequentially

* Corresponding author at: 280 South Chong Qing Road, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China. Tel.: +86 21 63846590x776491; fax: +86 21 54660873.
E-mail address: jmei@sjtu.edu.cn (J. Mi).

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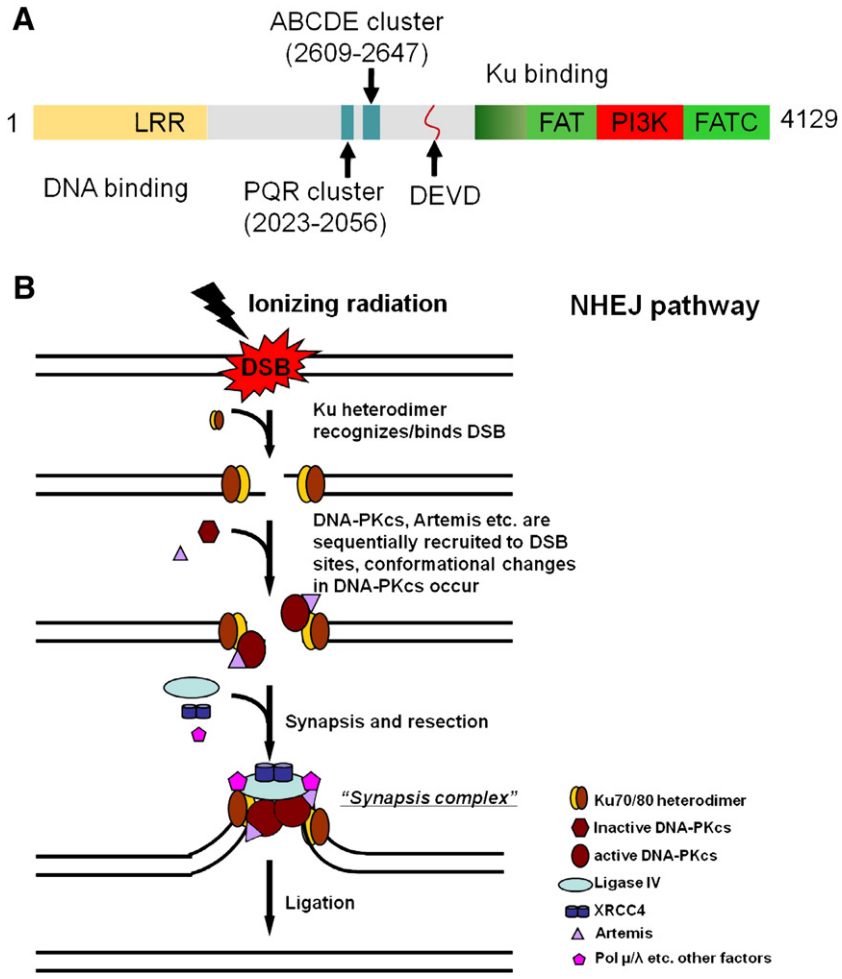

Fig. 1. The central role of DNA-PK in NHEJ A. Schematic representation of DNA-PKcs. Except ABCDE and PRQ phosphorylation clusters, DNA-PKcs is comprised of ku-binding, DNA-binding, FAT, FATC and PI3K kinase domains. DNA-PKcs also contains a caspase 3 site (DEVD). B. The process of NHEJ. On the site of a DSB, DNA ends are recognized by ring-shaped Ku heterodimer, which attracts unphosphorylated DNA-PKcs. After tethering of the broken DNA ends, autophosphorylated DNA-PKcs forms a synapsis bridging two proximal broken DNA ends; in the mean time, Artemis, XRCC4, ligase IV etc. DNA repair enzymes are recruited to the DSB site, and effectively link two broken DNA end together, which is very important for chromosome integrity maintenance.

binds the −65 E-box of the FAS promoter. In addition, our recent finding suggests DNA-PK may regulate the homeostasis of cell proliferation. These explorations have revealed that DNA-PK has more important roles than originally thought, so it is necessary to re-evaluate the importance of DNA-PK.

2. The structure of DNA-PK

DNA-PK, a member of phosphatidylinositol-3-OH kinase (PI(3)K)-related protein family [1], is a holoenzyme consisting of a catalytic subunit (DNA-PKcs) and a heterodimer of Ku (Ku70/Ku80) proteins. The catalytic subunit of DNA-PK (DNA-PKcs) comprises of 4129 amino acids (about 469 kilodalton). The DNA-PKcs gene is located at 8q11 in human. Besides catalytic domain, DNA-binding and Ku-binding domains, DNA-PKcs also contain a Leucin-rich region (LRR), FAT (FRAP (FKBP12-rapamycin-associated protein), ATM (ataxiatelangiectasia mutated), TRRAP (transactivation/transformation-domain-associated protein)) domain, C-terminal of FAT domain (FATC) and two phosphorylation clusters (PQR and ABCDE) [2–4] (Fig. 1A). Heterodimer of Ku70/Ku80 consists of 609 amino acids and 732 amino acids respectively. Their genes are separately located on chromosomes 22q13 and 2q33–34 in human [5].

Previous studies have suggested a direct role of DNA-PKcs in promoting the synapsis of broken DNA ends [6,7], most probably by self-association of DNA-end-bound DNA-PKcs molecules. The three-dimensional (3D) structure of DNA-PK complex at 25 resolution as determined by single-particle electron microscopy has shown that the binding of Ku and DNA elicits conformational changes in the FAT and FATC domains of DNA-PKcs. Observed dimeric particles have two DNA-PKcs/Ku70/Ku80 holoenzymes interacting through the N-terminal HEAT repeats [8]. The proximity of two similar complex contacting to the DNA ends suggests that these synaptic complexes maintain broken DNA ends in proximity and provide a platform for access of the various enzymes required for end processing and ligation. A higher resolution structure (7 resolution) of DNA-PKcs determined by cryo-electron microscopy single-particle reconstruction has demonstrated that this structure is composed of density rods throughout the molecule that are indicative of helices [9]. Moreover, docking of homology models into the DNA-PKcs structure demonstrates that up to eight helical HEAT repeat motifs fit well within this density rods. Furthermore, the overall fold is clearly visible in the crystal structure of human DNA-PKcs at 6.6 resolution [10]. The numerous *a*-helical HEAT repeats (helix–turn–helix motifs) facilitate bending and allow the polypeptide chain to fold into a hollow circular structure. The carboxy-terminal kinase domain is located on top of this structure, and a small HEAT repeat domain that