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Review

The Ku heterodimer: Function in DNA repair and beyond

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ABSTRACT

Ku is an abundant, highly conserved DNA binding protein found in both prokaryotes and eukaryotes that plays essential roles in the maintenance of genome integrity. In eukaryotes, Ku is a heterodimer comprised of two subunits, Ku70 and Ku80, that is best characterized for its central role as the initial DNA end binding factor in the "classical" non-homologous end joining (C-NHEJ) pathway, the main DNA double-strand break (DSB) repair pathway in mammals. Ku binds double-stranded DNA ends with high affinity in a sequence-independent manner through a central ring formed by the intertwined strands of the Ku70 and Ku80 subunits. At the break, Ku directly and indirectly interacts with several C-NHEJ factors and processing enzymes, serving as the scaffold for the entire DNA repair complex. There is also evidence that Ku is involved in signaling to the DNA damage response (DDR) machinery to modulate the activation of cell cycle checkpoints and the activation of apoptosis. Interestingly, Ku is also associated with telomeres, where, paradoxically to its DNA end-joining functions, it protects the telomere ends from being recognized as DSBs, thereby preventing their recombination and degradation. Ku, together with the silent information regulator (Sir) complex is also required for transcriptional silencing through telomere position effect (TPE). How Ku associates with telomeres, whether it is through direct DNA binding, or through protein–protein interactions with other telomere bound factors remains to be determined. Ku is central to the protection of organisms through its participation in C-NHEJ to repair DSBs generated during V(D)J recombination, a process that is indispensable for the establishment of the immune response. Ku also functions to prevent tumorigenesis and senescence since Ku-deficient mice show increased cancer incidence and early onset of aging. Overall, Ku function is critical to the maintenance of genomic integrity and to proper cellular and organismal development.

Contents

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1. Introduction

Ku was first identified in the early 1980s as an autoantigen targeted by autoantibodies in the serum of patients diagnosed with an autoimmune disease known as scleroderma polymyositis overlap syndrome [1]. The name Ku comes from the first two letters of the name of the original patient in whose serum it was identified. Autoantibodies directed against Ku were subsequently found in several other autoimmune diseases, including systemic lupus erythematosus, Sjorgren's syndrome, polymyositis and scleroderma [2–4]. Early studies using serum from Ku-positive patients identified Ku as an abundant, mostly nuclear protein [1,5]. Subsequent reports showed that Ku had unusual DNA binding properties, binding avidly to the ends of double-stranded DNA molecules in a sequence-independent manner, and to a lesser extent, to other forms of DNA discontinuities such as hairpins gaps and nicks [5–7]. These unusual end-binding properties made Ku an appealing candidate for a role in DSB repair and V(D)J recombination, which was confirmed when the two Ku subunits (XRCC5, Ku80 and XRCC6, Ku70) were found to complement the DNA repair defect of several IR-sensitive cell lines [8–14]. It is now well established that while not essential to individual life in the short term, Ku function is critical to the maintenance of genomic integrity and to the proper cellular and organismal development. A better understanding of Ku's diverse roles at the cellular and organismal level have implications for the study and the treatment of other human diseases, such as immune system disorders, cancer and aging.

2. Ku structure

Ku is a highly abundant protein found *in vivo* as a stable heterodimer consisting of two subunits, Ku70 and Ku80 (70 and 80 kDa, respectively). Both Ku70 and Ku80 eukaryotic Ku subunits contain three domains (Fig. 1A): an N-terminal alpha helix/beta barrel von Willebrand A (vWA) domain; a central core domain

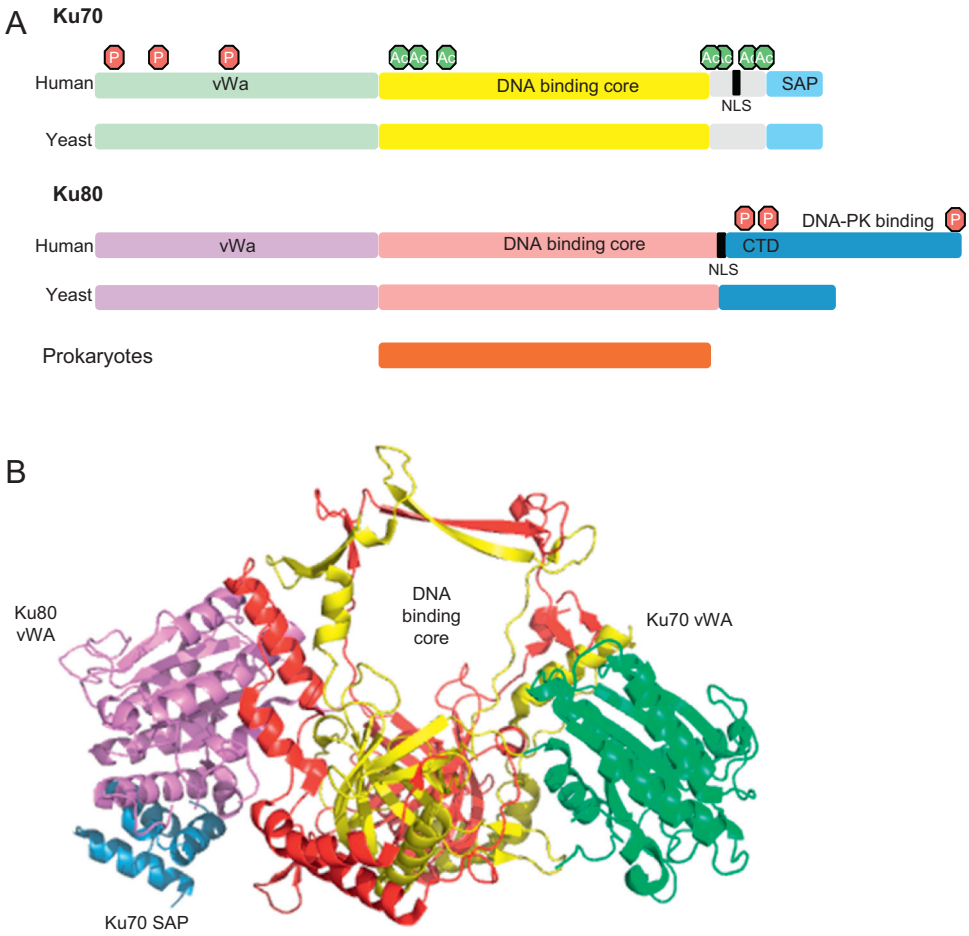

Fig. 1. Representation of Ku structure. (A) Schematic diagram of domain representation of the Ku70 and Ku80 subunits. The subunit domain structure of yeast and human Ku consists of the alpha helix, beta barrel N-terminal vWA domain, a central DNA binding core and a C-terminal helical domain (CTD). The eukaryotic Ku80 CTD contains the region required for binding DNA-PK_{CS}, while the Ku70 CTD is shorter and contains a SAF-A/B, Acinus and PIAS domain (SAP). The location of the nuclear localization signals and post translation modifications (phosphorylation and acetylation) on the human Ku protein is indicated. Yeast Ku is comprised of a similar domain structure to human Ku, except for a truncated C-terminal domain in Ku80. Prokaryotes encode for a single Ku subunit that is homologous to the eukaryotic core DNA binding domain. (B) The crystal structure of human Ku (PDB: IJEY) colored according to the domain structure. The dimer forms an asymmetrical basket structure with a positively charged ring large enough to accommodate two turns of the DNA. The Ku80 C-terminus is not included in this crystal structure.