Available online at www.sciencedirect.com
ScienceDirect
The International Journal of Biochemistry & Cell Biology 40 (2008) 598–603
IJBCB
www.elsevier.com/locate/biocel

Signalling networks in focus

# Ku, Artemis, and ataxia-telangiectasia-mutated: Signalling networks in DNA damage

Tomohiro Morio [a,1,2], Hyeyoung Kim [b,*,1]

[a] *Department of Pediatrics and Developmental Biology, Tokyo Medical and Dental University, Graduate School of Medicine, Tokyo 113-8519, Japan*
[b] *Department of Food and Nutrition, Brain Korea 21 Project, College of Human Ecology, Yonsei University, Seoul 120-749, Republic of Korea*

Received 15 September 2007; received in revised form 6 December 2007; accepted 17 December 2007
Available online 24 December 2007

**Abstract**

Cell death linked to DNA damage has been implicated in various diseases caused by environmental stress and infection. Severe DNA damage, which is beyond the capacity of the DNA repair proteins, triggers apoptosis. Accumulation of DNA damage has been proposed to be a principal mechanism of infection, inflammation, cancer, and aging. The most deleterious form of DNA damage is double-strand breaks (DSBs), where ataxia-telangiectasia-mutated (ATM) is the main transducer of the double-strand DNA break signal. Once the DNA is damaged, the DNA repair protein Ku70/80 translocates into the nucleus, a process which may be mediated by ataxia-telangiectasia-mutated, a member of the phosphoinositide-3-kinase-like family. The function and stability of Artemis may also be regulated by ataxia-telangiectasia-mutated through its phosphorylation upon the occurrence of DNA damage. Interestingly, both Artemis and Ku70/80 are substrates of DNA-dependent protein kinase (DNA-PK), another member of the phosphoinositide-3-kinase-like family. In this review, we show how Ku and Artemis function in the DNA damage response and the ataxia-telangiectasia-mutated signaling pathway and discuss potential applications of agents targeting these DNA damage response molecules in the treatment of inflammation and cancer.


*Keywords:* Ku; Artemis; Ataxia-telangiectasia-mutated; DNA damage

*Abbreviations:* AT, ataxia-telangiectasia; ATM, ataxia-telangiectasia-mutated; ATR, ataxia-telangiectasia and Rad3-related; DNA-PK, DNA-dependent protein kinase; DNA-PKcs, catalytic subunit of DNA-dependent protein kinase; DSBs, double-strand breaks; ROS, reactive oxygen species; NHEJ, non-homologous end joining; HR, homologous recombination; PI-3-kinase, phosphoinositide-3-kinase; CHK2, checkpoint 2 kinase; CdK, cyclin-dependent kinase; M/R/N complex, Mre11/Rad50/NBS1; ATRIP, ATR-interacting protein; XRCC4, X-ray repair complementing defective repair in Chinese hamster cells 4; Mre11, meiotic recombination 11; NBS1, Nijmegen breakage syndrome 1; MDM2, mouse double minute 2; H2AX, histone H2AX; IgCS, immunoglobulin class switch.

* Corresponding author. Tel.: +82 2 2123 3125; fax: +82 2 364 5781.
*E-mail addresses:* tmorio.ped@tmd.ac.jp (T. Morio), kim626@yonsei.ac.kr (H. Kim).
[1] Both the authors contributed equally to the work.
[2] Tel.: +81 3 5803 5245; fax: +81 3 5803 5245.

1357-2725/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.biocel.2007.12.007

**Signaling network facts**

- Ataxia-telangiectasia-mutated, Ku70/80, and Artemis are involved in the cellular pathways that work to repair DNA double-strand breaks.
- Ku70/80 and Artemis play a crucial role in non-homologous end joining by interacting with other molecules, such as X-ray repair complementing defective repair in Chinese hamster cells 4 (XRCC4), DNA ligase IV, and Cernunnos. Ataxia-telangiectasia-mutated plays a mediating role in homologous recombinational repair of DNA damage by interacting with meiotic recombination 11/Rad50/Nijmegen breakage syndrome 1.
- Functions of Ku70/80 and Artemis are, at least in part, controlled by phosphorylation by DNA-dependent protein kinase. Ku70/80 and Artemis are also substrates of ataxia-telangiectasia-mutated.
- The ataxia-telangiectasia-mutated signal is critical in cell cycle control and in cellular apoptosis via the p53 pathway.
- Ku proteins translocate into the nucleus upon the occurrence of DNA damage, and their nuclear transports are possibly controlled by phosphorylation.
- Nuclear loss of Ku proteins or ataxia-telangiectasia-mutated may be the underlying mechanism of oxidative stress-induced apoptotic cell death.

## 1. Introduction

Many types of DNA damage can occur within cells, but the most dangerous are double-strand breaks (DSBs). These results from exogenous agents (such as ionizing radiation, chemotherapeutic drugs, and infectious agents), endogenously generated reactive oxygen species (ROS), and mechanical stress acting on the chromosomes. DSBs can also be produced when DNA replication forks encounter DNA single-strand breaks or other lesions. Accumulation of DNA damage, leading to adult stem cell exhaustion, has been proposed as a principal mechanism of aging (Nijnik et al., 2007).

DNA repair proteins, such as DNA-dependent protein kinase (DNA-PK), Ku, and ataxia-telangiectasia-mutated (ATM), have been linked to cellular DNA repair pathways that work to fix DNA DSBs, while ataxia-telangiectasia and Rad3-related (ATR) is activated by many forms of DNA damage. Ku70/80 and Artemis are involved in non-homologous end joining (NHEJ) by interacting with other molecules, such as X-ray repair complementing defective repair in Chinese hamster cells 4 (XRCC4), DNA ligase IV, and Cernunnos. ATM is involved in homologous recombinational repair of DNA damage by interaction with meiotic recombination 11 (Mre11)/Rad50/Nijmegen breakage syndrome 1 (NBS1) (M/R/N complex), cell cycle arrest by the phosphorylation of various molecules such as checkpoint 2 kinase (CHK2), and cellular apoptosis via the p53 pathway.

ATM and DNA-PK may regulate the function of Ku70/80 and Artemis by phosphorylation and/or nuclear transport of Ku proteins and Artemis. In oxidative stress-induced DNA damage, ATM is essential for Ku activation and cell survival. The nuclear loss of Ku 70/80 or ATM is observed upon genotoxic stimuli. Degradation of these molecules may be another underlying mechanism of apoptosis. Further studies on the regulatory mechanisms and signaling networks of DNA damage response molecules are needed to better understand the complex cellular response. This review focuses on the interplay among ATM, Artemis, and Ku70/80 in response to DNA DSBs.

## 2. Key molecules and functions

### *2.1. Ku70/80 and DNA damage*

The Ku70 (70 kDa) and Ku80 (80 kDa) proteins are DNA-binding regulatory subunits of DNA-PK, which is composed of a 470 kDa catalytic subunit (DNA-PKcs) and Ku proteins. Ku70 and Ku80 initiate the repair process of DNA DSBs, which produce DNA fragmentation, by activating DNA-PK after binding to the DNA DSBs. In addition to the regulatory function of the Ku proteins in DNA-PK, heterodimers of Ku70 and Ku80 have independent DNA repair functions. These include single-stranded DNA-dependent ATPase activity and the binding and repair of broken single-stranded DNA, single-stranded nicks, gaps in DNA, and single-strand-to-double-strand transitions in DNA. The importance of Ku70/80 in DSBs is highlighted by the fact that Ku70-deficient cells have increased ionizing radiosensitivity, defective DNA end-binding activity, and impaired V(D)J recombination. Ku80-null mice display an increase in chromosomal aberrations and malignant transformation