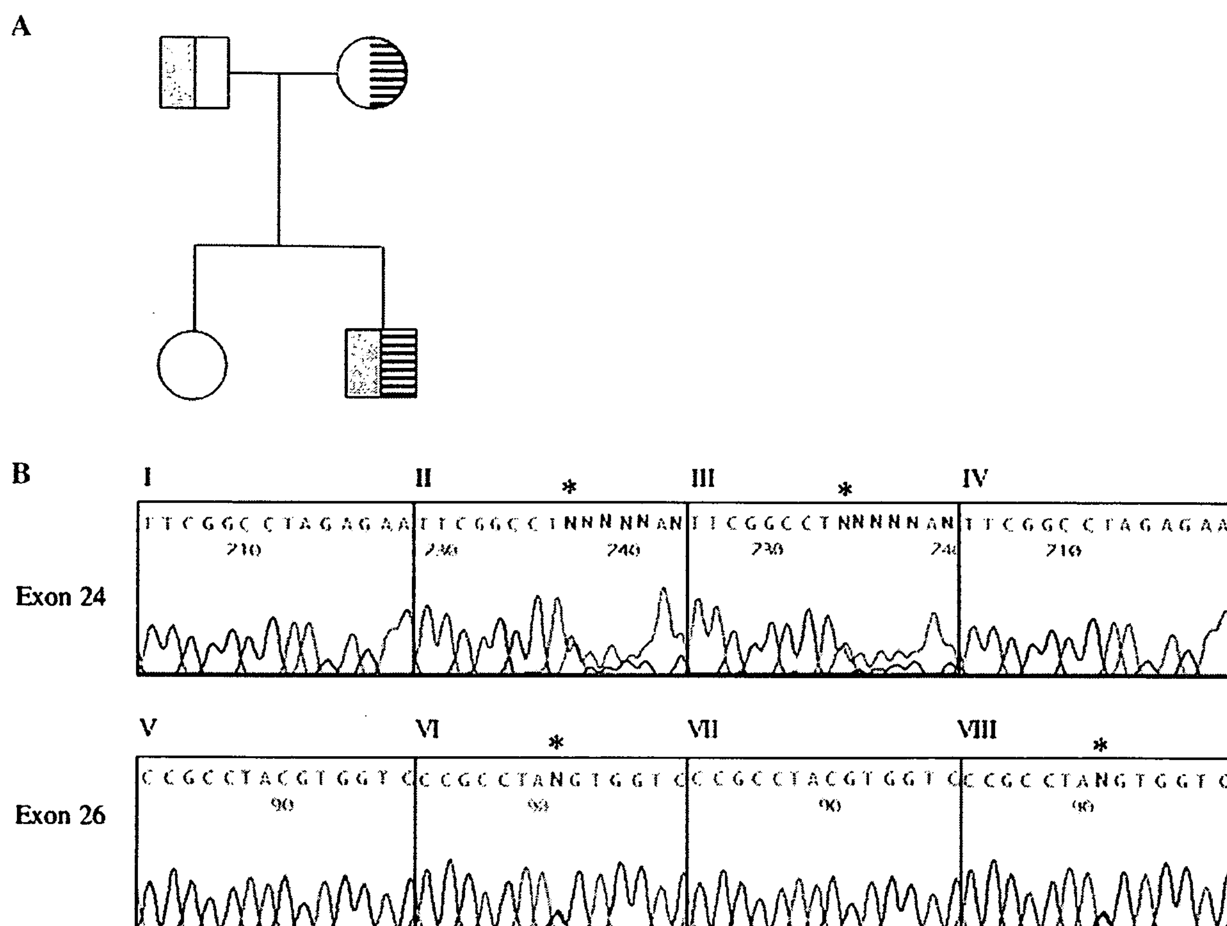

Fig. 1. (A) Pedigree of the family with C3 deficiency in this study. The patient was revealed to have compound heterozygous *C3* gene mutations with a paternal mutation (indicated as dark shadings) and a maternal mutation (indicated as horizontal strips). (B) Sequencing analysis of the patient with C3 deficiency and his family members I–IV: Sequence of a portion of exon 24 in the *C3* gene; normal individual (I), patient (II), patient's father (III) and patient's mother (IV). The mutation, derived from his father (indicated as dark shading in A) is a 1-bp insertion (3176insT) (asterisk mark indicates insertion point). V–VIII: Sequence of a portion of exon 26 in the *C3* gene; normal individual (V), patient (VI), patient's father (VII) and patient's mother (VIII). The mutation derived from his mother (indicated as horizontal strips in A) is a nonsense mutation described as C3303G (Y1081X) (asterisk mark indicates the mutated nucleotide).

affecting the different chains, can be compensated for by binding of the remaining wild type and the functionally normal α and β chains from the different alleles to avoid a more severe C3 deficiency. This hypothesis seemed consistent with the unexpected findings in hereditary C3 deficiency; its extremely rare occurrence and high ratio of homozygous mutation occurrence.

Case report

The pedigree of C3 deficiency is shown in Fig. 1A. The patient is a 2-year-old Japanese boy, who had suffered from several bacterial infections, such as meningitis, bronchitis and pneumonia. His parents and 5-year-old sister were all in good health. The parents were not related. Laboratory findings of the patient at this time were as follows: undetectable serum C3 level (<2 mg/dl; normal range, 75–150 mg/dl) and low CH50 (<12 U/ml; normal range, 35–45 U/ml). Blood examination of family members revealed that their serum C3 levels were 46 mg/dl in the father, 51 mg/dl in the mother and normal level in the sister, respectively. Serum CH50 levels were 33 U/ml in the father and 23 U/ml in the mother. Serum C4 levels in these family members were all within the normal range.

Materials and methods

Informed consent was obtained from his parents. Genomic DNA from family members, as well as from control individuals, was PCR-amplified for over the entire coding sequence of the *C3* gene including all its exon–intron boundaries using appropriate primers. PCR amplification products were purified using a QIAEX II Gel Extraction Kit (Qiagen) and directly sequenced in both directions using ABI PRISM 310 Genetic Analyzer (Applied Biosystems, Foster City, CA, USA).

Results and discussion

The patient was shown to have compound heterozygous *C3* gene mutations as shown in the Fig. 1B. They were a novel one base insertion (3176insT) in exon 24 which is predicted to result

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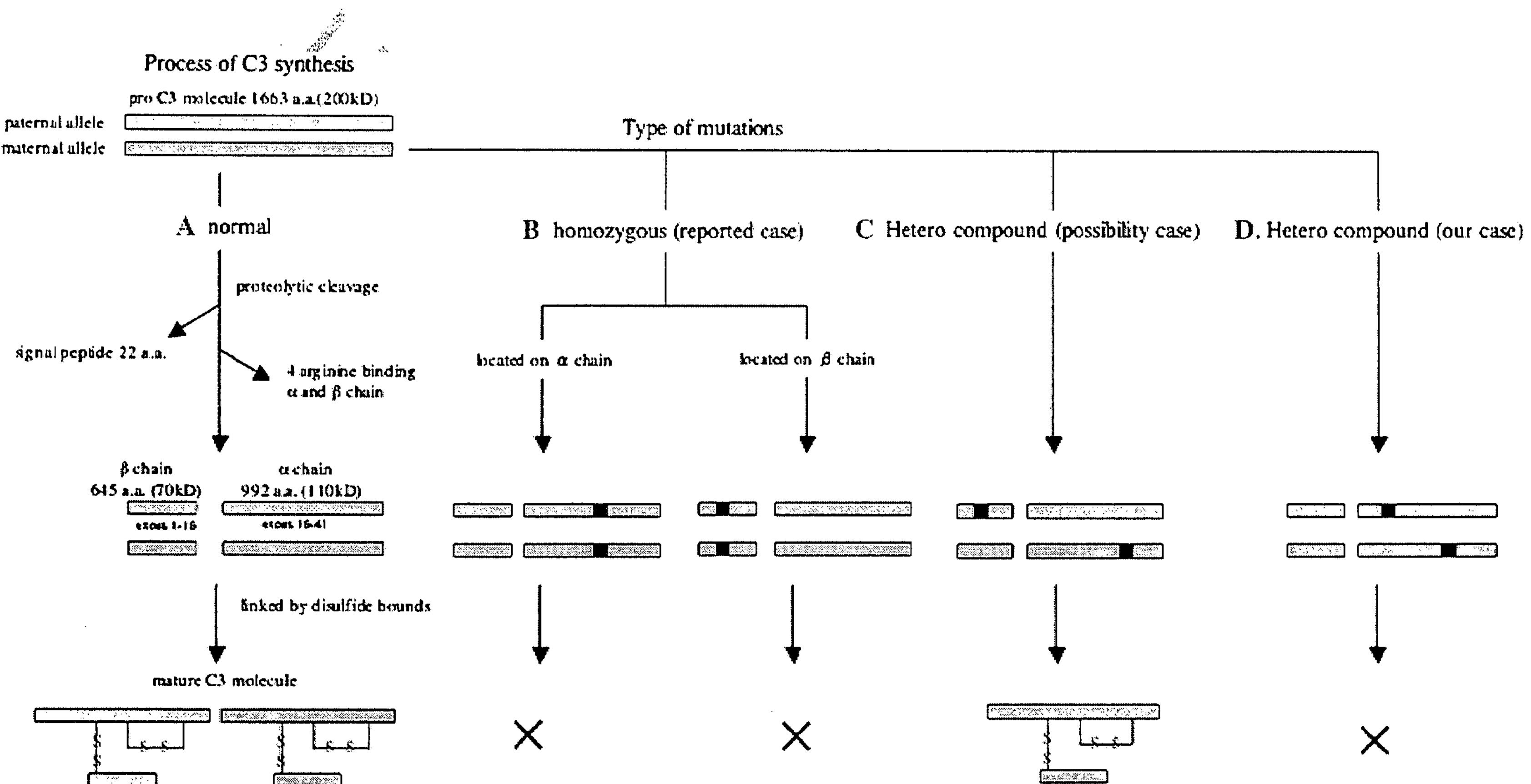

Fig. 2. The proposed hypothesis with regard to the mechanism of C3 deficiency based on the unique process of C3 synthesis. (A) Normal synthesis of the mature C3 molecule. (B–D) Various combinations of the *C3* gene mutations. (B) Homozygous mutations in the *C3* gene. No functional mature C3 molecule can be produced because both mutations ruin the same chains. (C) Hypothetical case: in some combinations of mutations in the different allele, a mature C3 molecule could be produced from functional α and β chains from the different allele. (D) Our case with compound heterozygous *C3* gene mutations: In both the mutations located in the same C3 α chain, no functional C3 molecule can be produced.

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in a frameshift and a premature downstream stop codon (K1105X) in exon 26, and a nonsense mutation of C3303G (Y1081X) in exon 26, which was previously reported as homozygous mutations elsewhere [7]. These defects were not found in any unaffected family members or in 100 healthy control individuals. Both patient's PCR fragments (exon 24 and exon 26) were ligated to pCR2.1 TA cloning vector (Invitrogen, Carlsbad, CA, USA) and transformed INVαF′ (Invitrogen, Carlsbad, CA, USA) competent cells for confirming the mutant clone sequence. It is noted that both the mutations are predicted to result in a truncation of the α chain of the C3 molecule. This finding may be linked to the unique process of C3 synthesis. The *C3* mRNA is translated into a signal peptide precursor form of pro-C3 molecule from each allele (paternal and maternal alleles), and subsequently processed by proteolytic cleavage into the β chain (13 kb from exons 1–16) and the α chain (28 kb from exons 16–41) [10], which are cross-linked by disulfide bonds to make the mature C3 molecule (Fig. 2A). Almost all cases with C3 deficiency have been reported as homozygous mutations in the *C3* gene. No functional mature C3 molecule can be produced (Fig. 2B). ~~Thus, the hypothesis is as follows;~~ a possible case without C3 deficiency in spite of harboring compound heterozygous *C3* gene mutations. The functional α and β chains from the different allele can be recombined to avoid severe deficiency (Fig. 2C) with the exception of nonsense mutation in β chain, in this case neither the functional α nor β chains could be synthesized from one allele with nonsense mutation. Although our case is an exceptional one with compound heterozygous *C3* gene mutations, no functional C3 can be produced (Fig. 2D). Thus, although this is the first exceptional case with heterozygous *C3* gene mutations confirmed, it is still consistent with our hypothesis. Moreover, though there might be a patient having gene mutations such as Fig. 2C, he or she avoids severe deficiency for existence of the functional α and β chains, as a result it might not be detected as C3 deficiency. The reason why the C3 deficiency is an extremely rare disease and for the high ratio of homozygous mutation occurrence might be based on such backgrounds. Further studies, for more cases with C3 deficiency that have been characterized at the molecular level, will be needed to confirm this hypothesis.

Uncited reference Q2

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Signaling networks in focus

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

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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.
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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.

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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

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(Difilippantonio et al., 2000; Gu, Jin, Gao, Weaver, & Alt, 1997).

Ku70/80 plays a critical role in the repair of damaged DNA through NHEJ by interacting with XRCC4, Cernunnos, and DNA ligase IV. Phosphorylation of Ku70/80 by DNA-PK controls their localization, DNA binding, and function. DNA-PK phosphorylates Artemis, p53, and histone H2AX, which determine the fate of the cells.

Oxidative stress can be caused by ionizing radiation, cytotoxic drugs, infection, inflammation, cancer, and aging. It leads to the generation of single-strand breaks and DSBs. Oxidative stress-induced DNA damage of haematopoietic stem cells during aging is repaired mainly by NHEJ, in which Ku70/80 has a critical role, but ATM may also be involved (Nijnik et al., 2007). Oxidative injury caused by mild ischemia/reperfusion in the spinal cord induces reversible neurological deficits with increased Ku-DNA binding activity, whereas severe ischemia/reperfusion causes permanent deficits that are accompanied by a decrease in the Ku-DNA binding activity. Therefore, Ku may have a protective role against oxidative injury (Shackelford, Tobaru, Zhang, & Zivin, 1999). Embryonic fibroblasts derived from Ku80-null mice are more susceptible to DNA damage than those from wild-type mice (Arrington et al., 2000), suggesting that a decrease in Ku may be involved in the mechanism of apoptotic cell death. DNA-PKcs is the substrate for caspase-3, which is activated by ischemia/reperfusion and ROS. The reduction in Ku might be induced in a caspase-activating apoptotic pathway after ischemia/reperfusion (Shackelford et al., 1999). Nuclear localization of Ku70 and Ku80 are mediated by two compartments of the nuclear pore-targeting complex, importin α and importin β. Oxidative stress-induced apoptosis is mediated by the activated caspase-3, which degrades Ku70/80 (Song, Lim, Kim, Morio, & Kim, 2003). A decrease in Ku binding to nuclear transporters importin α and importin β results in reduced levels of nuclear Ku70/80 in pancreatic acinar cells. Further studies are required to determine the mechanism of selective reduction of each Ku component upon the occurrence of DNA damage in the cells.

2.2. *Ku70/80 as a signaling molecule*

Ku70/80 are located in the cytoplasm and on the cell surface (Morio et al., 1999). Ku70 serves as a receptor for *Rickettsia conorii* internalization (Martinez, Seveau, Veiga, Matsuyama, & Cossart, 2005). Ku70/80 is associated with CD40 in the cytoplasm, and CD40 engagement leads to the translocation of Ku70/80 to the cell surface of multiple myeloma cells. In normal human B cells, Ku70/80 resides in the cytoplasm and translocates to the nucleus upon the receipt of the immunoglobulin class switch (IgCS)-inducing signal or upon DNA damage. Since B cells need NHEJ mediated by Ku70/80 when they undergo IgCS (Morio et al., 1999), Ku70/80 may act as a signaling molecule in this cellular process.

Modification of Ku70 and Ku80 takes place when DNA is damaged, and the functional consequences of this modification are of particular interest. Polyglutamine (polyQ) diseases, such as Huntington's disease and Machado-Joseph disease, are caused by the gain of a toxic function by abnormally expanded polyQ tracts. An expanded polyQ of ataxin-3, a gene that causes Machado-Joseph disease, stimulates Ku70 acetylation. This post-translational modification of Ku70 dissociates the proapoptotic protein Bax from Ku70, thereby promoting Bax activation and subsequent cell death. This suggests that cell death is, at least in part, controlled by acetylation of Ku70 (Li et al., in press). The physiological relevance of Ku phosphorylation is still an enigma. There are four DNA-PK phosphorylation sites on the Ku70/80 heterodimer: serine 6 of Ku70, serine 577 and 580 and threonine 715 of Ku80. However, neither DNA-PK nor ATM is required for phosphorylation of these sites on the Ku70/80 heterodimer *in vivo*. DNA-PK-dependent phosphorylation of Ku70/80 is not required for NHEJ either. The involvement of ATM in Ku70/80 modification awaits further study.

2.3. *ATM and Ku70/80*

ATM is the protein product of the gene mutated in the multisystem disorder ataxia-telangiectasia (AT), which is characterized by neuronal degeneration, immunodeficiency, chromosomal instability, and a predisposition to cancer formation. ATM is a large molecule with serine/threonine kinase activity, and it functions in DNA damage responses and cell cycle control. DSB recognition is the first step in the DSB damage response and involves activation of ATM and phosphorylation of targets, such as p53, to trigger cell cycle arrest, DNA repair, or apoptosis. The activation of ATR kinase by DSBs also occurs in an ATM-dependent manner. On the other hand, Ku70/80 is known to participate at a later time in the DSB response, recruiting DNA-PKcs to facilitate NHEJ. Recent finding shows that Ku70/80 plays a novel role in modulating ATM-dependent ATR activation during the DSB damage response and confers a protective effect against ATM-independent ATR activation at later stages of the DSB damage response (Tomimatsu et al., 2007). Following exposure to genotoxic stress, proliferating cells actively slow down DNA

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replication through an S phase checkpoint to provide time for repair. The ATM-dependent pathway plays an important role in the S phase checkpoint response following ionizing radiation. Stronger S checkpoint activity in irradiated Ku80-null cells is due to the higher ATM kinase activity. Ku affects the ATM-dependent S phase checkpoint following ionizing radiation (Zhou et al., 2002). Ionizing radiation exposure results in the upregulation of Ku70 via a p53/ATM-dependent mechanism. Increased oxidative stress has been reported in neuronal tissues of ATM-deficient mice (Kamsler, Daily, Hochman, Stern, & Shiloh, 2001). It is not clear whether ATM itself is directly involved in sensing the increase in ROS or whether oxidative stress in AT cells is associated with unrepaired DSBs continuously present in the DNA. Transfecting AT cells with the full-length ATM gene assures cell death prevention, which may be assisted by the activation of Ku in response to oxidative stress (Lee, Kim, Morio, & Kim, 2006). ATM may be essential for Ku activation in the process of repairing DNA damage and preventing cell death.

2.4. ATM and Artemis

Artemis was originally identified as deficient in human radiosensitive severe combined immunodeficiency syndrome. Artemis exhibits an intrinsic single strand-specific 5′ to 3′ exonuclease activity and has hairpin-opening endonuclease activity, which is induced by phosphorylation by DNA-PK. Artemis has roles in V(D)J recombination, NHEJ, and regulation of the DNA damage-induced G2/M cell cycle checkpoint. Cells with mutations in the Artemis gene and Artemis-deficient cells exhibit radiosensitivity and defective V(D)J recombination, implicating the Artemis function in NHEJ (Wang et al., 2005). Since the NHEJ reaction functions as a genomic caretaker, particularly in the prevention of translocations and telomere fusions, Artemis deficiency may be related to carcinogenesis.

The *bona fide* phosphorylation sites and physiological relevance of the phosphorylation are, however, still under investigation. Three basic phosphorylation sites (S385, S516/518) and 11 DNA-PK phosphorylation sites were identified by proteomic analysis using matrix-assisted laser desorption/ionization-time of flight mass spectrometry (MALDI-TOF MS). There were nine other putative DNA-PK/ATM phosphorylation sites identified. Most of the phosphorylation sites are clustered in the C-terminus region. It is now evident that Artemis is a downstream component of the ATM signaling pathway; ATM is the major kinase responsible for the modification of Artemis (Poinsignon et al., 2004; Riballo et al., 2004; Zhang et al., 2004). One of the target sites of ATM is S645 of Artemis, and its phosphorylation leads to hyperphosphorylation of Artemis. Artemis phosphorylation by ATM is important in association with the M/R/N complex and Cdk1-cyclin B activation, which in turn controls G2/M checkpoint recovery. On the other hand, phosphatase-treated mammalian Artemis still retains endonuclease activity. Artemis molecule lacking the C-terminal domain is sufficient to complement V(D)J recombination in Artemis-null cells. How endonuclease activity of Artemis and its association with the damaged termini are controlled is still controversial. DNA-PK, ATM, and other not-yet-identified kinase(s) could be involved in the pathway leading to Artemis activation.

3. Cascades

As for DSBs, ATM phosphorylates key proteins in the salvage pathways leading to DSB repair and activation of cell cycle checkpoints (Fig. 1). DNA repair proteins interact with other molecules to repair the damaged DNA through NHEJ or homologous recombination (HR). For instance, ATM phosphorylates key proteins (Ku70/80 and Artemis) to repair the damaged DNA by NHEJ. On the other hand, ATM temporarily arrests the cell cycle by phosphorylating CHK2, which in turn phosphorylates p53, while the damage is being repaired. ATM repairs the damaged DNA through HR by interacting with ATR and the M/R/N complex. When the attempt to repair the

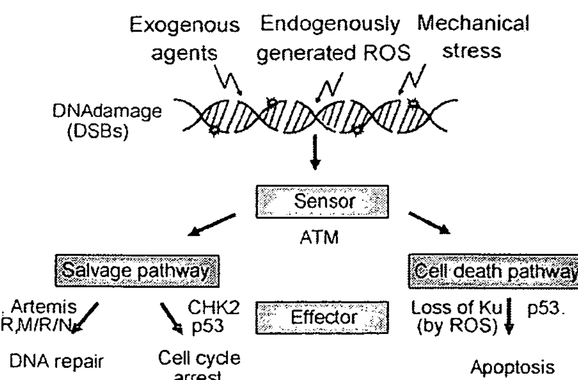

Fig. 1. Cell responses to DNA damage. Upon the formation of DSBs, ATM serves as a sensor for DNA damage and phosphorylates key proteins in pathways leading to DSB repair or the activation of cell cycle checkpoints. ATM phosphorylates key proteins (Ku70/80, Artemis) to repair the damaged DNA. Additionally, ATM temporarily arrests the cell cycle by phosphorylating CHK2, which in turn phosphorylates p53, while the damage is being repaired. ATM repairs the damaged DNA through HR by interacting with ATR and the M/R/N complex. When the attempt to repair the damage fails, the cell undergoes apoptosis via the p53 pathway. Oxidative stress-induced cell death stems from the nuclear loss of Ku70/80.

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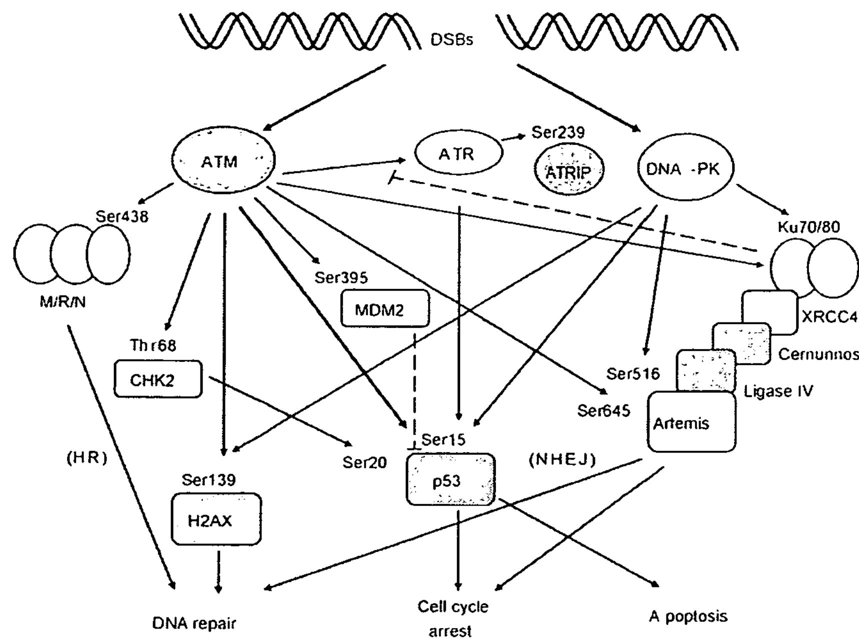

Fig. 2. Targets for the ATM/DNA-PK phosphorylation and signaling network. DNA-PK, ATM, and ATR are recruited to the sites of DNA damage through analogous mechanisms involving conserved interaction motifs observed in Ku80, NBS1, and ATRIP, respectively. Ku70/80 and Artemis play critical roles in the repair of damaged DNA through NHEJ by interacting with XRCC4/Cernunnos/DNA ligase IV. Phosphorylation of Ku70/80 and Artemis by DNA-PK and ATM controls cell cycle arrest and the DNA repair function. ATM triggers the repair of damaged DNA through HR by interacting with the M/R/N complex. ATM phosphorylates CHK2, which phosphorylates p53 to arrest the cell cycle, while damage is being repaired. When the attempt to repair the damage fails, the cell undergoes apoptosis via the p53 pathway. Dotted lines: Ku70/80 also affects ATM-dependent ATR activation. The stability of p53 is also tightly controlled by MDM2.

264 damage fails, the cell undergoes apoptosis via the p53 pathway. Oxidative stress-induced cell death stems from the nuclear loss of Ku70/80 (Song et al., 2003).

267 As shown in Fig. 2, DNA repair is mediated by DNA damage response molecules and involves three members of the phosphoinositide-3-kinase-like family (ATM, ATR, and DNA-PK). DNA-PK, ATM, and ATR are recruited to the sites of DNA damage through analogous mechanisms involving conserved interaction motifs observed in Ku80, NBS1, and ATRIP, respectively. The DNA-PK/Ku70/80 complex is required for the NHEJ DNA repair pathway. Artemis plays a role in processing the DNA ends prior to ligation. XRCC4/Cernunnos/DNA ligase IV is recruited to the DNA-PK/Ku complex, which is required for end joining. ATM plays a role in DNA DSB repair in concert with the M/R/N complex. DNA-PK and ATM share several substrates as phosphorylation targets, including Artemis, p53, and histone H2AX. Interplays among Ku70/80, Artemis, DNA-PK, and ATM are involved in DNA damage responses. Ku70/80 also affects ATM-dependent ATR activation. Degradation of key signaling molecules (p53, Ku70/80, and Artemis) is one of the mechanisms determining cell fate. Oxidative stress-induced degradation of Ku70/80 is mediated by caspase-3 (Song et al., 2003). Activity of p53 is regulated by the ubiquitin–proteasome system, which is the major non-lysosymal system for degrading proteins in the cell (Thompson et al., 2007). It is still unclear whether Ku70/80 and Artemis are similarly regulated by proteasome-dependent degradation or other protease systems. Degradation of Ku70/80 leads to upregulation of p53, resulting in apoptosis. The stability of p53 is also tightly controlled by mouse double minute 2 (MDM2) (Fig. 2).

4. Associated pathologies and therapeutic implications

Nuclear loss of Ku70/80 and DNA damage linked to oxidative stress in pancreatic acinar cells has been suggested as pathophysiologic mechanisms of pancreatitis (Song et al., 2003). DNA-PK deficiency in cultured neurons causes an accumulation of DNA damage and increased susceptibility to apoptosis (Chechlacz, Vemuri, & Naegele, 2001). Diminished DNA DSB repair by NHEJ causes a progressive loss of haematopoietic stem cells and bone marrow cellularity during aging (Nijnik et al., 2007). Therefore, the loss of function of Ku proteins and DNA-PK activity might be one of

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the important pathological mechanisms in apoptotic cell death related to pancreatic inflammation, neurological disorders, and aging. Since ATM is essential for nuclear Ku activation, maintenance of Ku70/80 and DNA-PK together with ATM may prevent DNA damage in various diseases and inflammation. Artemis serves as a tumor suppressor and patients with hypomorphic mutations in Artemis have a predisposition to develop lymphoma (Moshous et al., 2003). Phosphorylation and degradation of Artemis may be a key step in controlling cellular apoptosis and carcinogenesis. The formation of carcinogenic translocations requires the illegitimate joining of chromosomes containing DSBs. The molecules presented in this review are critical in DNA repair, and their defective function, improper localization, and loss may lead to unrepaired DNA DSBs and to the malignant transformation of cells when they escape apoptosis. The manipulation of these DNA damage response molecules could lead to anti-inflammatory agents and anti-cancer agents.

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