The ATM protein: The importance of being active

Yosef Shiloh and Yael Ziv

The David and Inez Myers Laboratory for Cancer Genetics, Department of Human Molecular Genetics and Biochemistry, Sackler School of Medicine, Tel Aviv University, Tel Aviv 69978, Israel

The ataxia telangiectasia mutated (ATM) protein kinase regulates the cellular response to deoxyribonucleic acid (DNA) double-strand breaks by phosphorylating numerous players in the extensive DNA damage response network. Two papers in this issue (Daniel et al. 2012. J. Cell Biol. http://dx.doi.org/10.1083/jcb201204035; Yamamoto et al. 2012. J. Cell Biol. http://dx.doi.org/10.1083/jcb201204098) strikingly show that, in mice, the presence of a catalytically inactive version of ATM is embryonically lethal. This is surprising because mice completely lacking ATM have a much more moderate phenotype. The findings impact on basic cancer research and cancer therapeutics.

Maintenance of genomic stability is essential for prevention of undue cell death or neoplasia (Cassidy and Venkitaraman, 2012). Critical DNA lesions, such as double-strand breaks (DSBs), activate the DNA damage response (DDR)—a widespread signaling network that involves DNA repair, activation of cell cycle checkpoints, and extensive modulation of gene expression and many metabolic pathways (Ciccia and Elledge, 2010; Hiom, 2010). DSBs are induced by ionizing radiation, radiomimetic chemicals, and endogenous oxygen radicals. They accompany replication fork stalling and are formed and resealed in meiotic recombination and the rearrangement of the antigen receptor genes during the development of the immune system. Major repair pathways for DSBs are error-prone non-homologous end joining (NHEJ) or high-fidelity homologous recombination repair (HRR; Holthausen et al., 2010; Lieber, 2010). The broad, powerful signaling network evoked by DSBs begins with rapid accumulation at DSB sites of a large group of proteins dubbed “sensors” or “moderators” and continues with the activation of several protein kinases (“transducers”) with partially redundant functions that relay the signal to numerous downstream effectors, which are typically key players in the various DDR branches (Lovejoy and Cortez, 2009; Ciccia and Elledge, 2010; Lukas et al., 2011).

The primary transducer of the DSB alarm is the serine-threonine kinase ataxia telangiectasia (A-T) mutated (ATM; Banin et al., 1998; Canman et al., 1998), which is activated in response to DSB induction (Bakkenist and Kastan, 2003) and goes on to phosphorylate a plethora of substrates (Matsuoka et al., 2007; Bensimon et al., 2010). ATM belongs to a conserved family of phosphoinositide 3-kinase–like protein kinases (PIKKs) that includes, among others, two other major DDR transducers: the catalytic subunit of the DNA-dependent protein kinase catalytic subunit (DNA-PKcs) and ATR (ataxia telangiectasia and Rad3 related). These three kinases maintain close functional relationships (Lovejoy and Cortez, 2009). Recent evidence suggests that ATM’s broad capacity as a protein kinase enables it to regulate other processes, such as oxidative stress levels (Guo et al., 2010), and play a role in cytoplasmic, non-DDR arenas, among them mitochondrial homeostasis (Yang et al., 2011; Valentín-Vega and Kastan, 2012; Valentín-Vega et al., 2012).

Human germline mutations that abrogate cellular responses to DNA damage cause severe genomic instability syndromes (Jeppesen et al., 2011). The ATM gene is mutated in the genomic instability syndrome, A-T (Savitsky et al., 1995). A-T is characterized by progressive neurodegeneration, immunodeficiency, cancer predisposition, genomic instability, and sensitivity to DSB-inducing agents (McKinnon, 2012). The disease is caused by null ATM mutations, and the patients usually exhibit complete loss of the ATM protein (Gilad et al., 1996).

Studies of ATM-dependent processes typically rely on human wild-type versus A-T cells, ATM knockdown using RNAi, reconstitution of ATM-deficient cells by ectopic expression of wild-type or kinase-dead ATM protein, or treating cultured cells with ATM inhibitors. Laboratories using these experimental systems have long felt that the physiological consequences of ATM loss as opposed to harboring inactive ATM may not be similar (Choi et al., 2010). The papers by Daniel et al. and Yamamoto et al. (both in this issue) provide solid evidence of this notion and mark a turning point in our view of ATM’s mode of function. Both works are based on manipulating the Atm gene in the mouse.

Atm knockout mice have long been around. These mice exhibit most of the symptoms of A-T, including low body weight, sterility, radiosensitivity, and cancer predisposition, but neurodegeneration is considerably less marked in these animals compared with that observed in human A-T patients (Barlow et al., 1996; Elson et al., 1996; Xu et al., 1996; Borghesani et al., 2000). Thus, before cancer emergence and without

Correspondence to Yosef Shiloh: yossih@post.tau.ac.il
It appears, therefore, that the presence of physiological levels of inactive Atm severely interferes with the DDR, certainly more than its absence. Why could this be? Although the exact mechanism of this phenomenon is unknown, some assumptions can be made. ATM is recruited to DSB sites (Andegeko et al., 2001) and is therefore present in the huge nuclear foci spanning these sites. Many ATM-mediated phosphorylations occur within these protein conglomerates. Importantly, the recruitment of kinase-dead Atm to sites of DNA damage was found by Daniel et al. (2012) and Yamamoto et al. (2012) to occur normally. It is possible that the presence of catalytically inactive Atm within these DDR hubs severely disturbs the ability of the cell to respond to the damage. Presumably, it interferes with the ordered temporal dynamics of events within these protein factories (Lukas et al., 2011). Deeper understanding of the spatial organization of these protein assemblies (Chapman et al., 2012) and the temporal hierarchy of events within them may elucidate ATM’s role not only as an enzyme but also as a protein moiety in these structures. Of note, ATM is a large protein of 3,056 residues, of which ~10% constitute its active site. The regulatory functions of the remaining 90% of this polypeptide are largely elusive. In a broader sense, these studies convincingly show, at the organismal level, that loss of an enzyme versus having it residing inactive in the cell can be worlds apart. In this context, it would be interesting to monitor the development of malignancies in those animals expressing the mutant Atm in their lymphoid system. This is particularly important because the malignancies observed in Atm−/− mice, similar to A-T patients, are primarily lymphoid.

The implications for ATM-related translational research are notable. ATM has naturally been considered a potential target to be inactivated in tumor cells to selectively sensitize them to radiotherapy (Begg et al., 2011; Basu et al., 2012; Golding et al., 2012). The advent of efficient ATM inhibitors (Hickson et al., 2004; Golding et al., 2009) has further spurred these hopes. The good news is that the effect of these inhibitors on cellular radiosensitivity (and, probably, general well being) might be more profound than previously estimated, provided that these small molecules could be targeted specifically into the malignant cells. On the other hand, exposure of normal, proliferating body tissues to ATM inhibitors may be undesirable, depending on the type of tissue. Such exposure of normal tissue to ATM inhibition, even if brief, could lead to substantial genomic instability—a potential driving force toward new malignancy.

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