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ATM mutation and radiosensitivity: An opportunity in the therapy of mantle cell lymphoma

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ABSTRACT

ATM (ataxia telangiectasia mutated) is a DNA damage signaling-initiation kinase which has diverse function in responding to genotoxic stress to maintain its genomic integrity. Cells harboring loss-of-function ATM deficiencies demonstrate extreme radiosensitivity. The scope of radiotherapy has been considered very limited among patients with biallelic mutations or deletions of ATM due to its toxic effect on normal tissue. Mantle cell lymphoma (MCL) is a highly chemo-refractory tumor with generally poor outcome, especially if the patients develop resistance to frontline drugs. ATM is the most frequently mutated gene in MCL and recent experimental evidence demonstrated that this mutational status can be taken advantage of using radiotherapy. Radiotherapy should be considered in the treatment of mantle cell lymphoma with a curative intent.

1. Introduction

Ataxia-telangiectasia mutated (ATM) is a protein coding gene for the ATM serine/threonine kinase located on chromosome 11q22-q23. ATM is the causative gene for the disease ataxia telangiectasia, in which biallelic gene inactivation results in a wide variety of symptoms that include ataxia, telangiectasia, radiosensitivity, insulin resistance, predisposition to lymphoid malignancy and immunodeficiency (Kastan et al., 2001). ATM carriers often exhibit radiosensitivity and higher risk of cancers (van Os et al., 2016; Thompson et al., 2005; Helgason et al., 2015). Of the lymphoid malignancies, T-cell acute lymphoblastic leukemia and non-Hodgkin's lymphoma (NHL) is reported among patients with ataxia telangiectasia (Murphy et al., 1999; Olsen et al., 2001; Ehrlich

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et al., 2015). In this review, we focus on the therapeutic implications of ATM mutation among patients with mantle cell lymphoma (MCL), a NHL with generally poor prognosis. We explore ways to target this mutational characteristic for the treatment of MCL.

2. Functions of ATM: the past and the present

ATM is a DNA damage sensor gene (Maréchal and Zou, 2013). It encodes for a phosphoinositide-3 (PI3) serine-threonine kinase family member in the nucleus (Shiloh and Ziv, 2013). To date the established functional role of ATM is that it acts as a signaling initiation kinase through phosphorylation of multiple downstream targets (Shiloh, 2003, 2001). DNA damage-induced ATM activation triggers signaling cascades which ultimately gives rise to two major outcomes: activation of DNA damage checkpoints (Abraham, 2001) to attenuate cell cycle progression and recruitment and modulation of enzymatic activities that process DNA damage, such as DNA double strand breaks (DSB) (Khanna et al., 2001). DSBs are the most lethal form of DNA lesions which can be generated by ionizing radiation and a large variety of DNA-damaging drugs (Canman et al., 1998). Efficient and accurate repair of DSBs is imperative for the cells to maintain chromosomal stability. Following a DSB, ATM coordinates complex cascades of events involving multiple cellular pathways (Banin et al., 1998) (Fig. 1). These events are sequentially organized as "sensors" which involve in the initial processing and recognition of DSBs. DNA damage signals, in the form of post-translation modifications such as phosphorylation, ubiquitylation, and PARylation (Brown and Jackson, 2015), are amplified and relayed to "transducers" and ultimately orchestrate the "effector" molecules (Shiloh and Ziv, 2013; Guleria and Chandna, 2016). While ATM acts early in response to DNA strand breaks, its functions projects broadly in the cellular response to genotoxic stress (Weizman et al., 2003). (Illustration reproduced courtesy of Cell Signaling Technology, Inc. (www.cellsignal.com)).

In additional to ATM, two other PI3K-like protein kinases also play critical and partially overlapping roles in DNA damage response. They are the ATR (ATM and RAD3-related) (Abraham, 2001) and DNA dependent protein kinase catalytic subunits (DNA-PKc) (Shiloh and Ziv, 2013; Durocher and Jackson, 2001; Falck et al., 2005). Together with ATM, they form the "PIKK trinity" and function as a complementary group to initiate and regulate DNA damage response that encompasses all types of genotoxic stress and also participate in cell proliferation, regulation of oxidative stress, cell signaling and cellular homeostasis (Shiloh, 2003; Gatei et al., 2001). There are hundreds of proteins that act as substrates to the PIKKs (Matsuoka et al., 2007), constituting a sophisticated stress response network. Deficiencies in any of these signaling kinases render cells highly susceptible to DNA damage and predispose individuals to cancer development. Fig. 1 illustrates the activation of the sensory DNA-PKc, ATM and ATR kinases that relay to two parallel cascades-the first cascade involves CHK kinases and the second one involves phosphorylation of p53. Ultimately, these pathways serve to inactivate cyclin B- CDC2 complex and prevent cells with DNA damage to enter mitosis.

3. ATM and radiosensitivity

Cells deficient in ATM show increased sensitivity to ionizing radiation. Compared to normal cells, rejoining of damaged chromosomes in response to radiation is five to six times less among ATM deficient cells (Cornforth and Bedford, 1985). ATM deficient cells also have slower rate of DSB repair and are not able to slow down their cell cycle progression, resulting in a characteristic ATM phenotype termed RDS (Radiation Resistant Synthesis) (Hickson et al., 2004; Chen et al., 2007). Thus tumor cells that lack ATM function, either through mutation or via pharmacological inhibition should be prone to radiotherapy because of their failure to initiate and coordinate repair mechanisms. On the other hand, inhibiting ATM in normal cells had led to catastrophic consequences. Patient with ataxia telangiectasia who developed lymphoma and were subjected to radiation, manifested severe mucositis of the esophagus and skin desquamation (Gotoff et al., 1967). The concern of insurmountable normal tissue toxicity has long been prohibitive for using radiation therapy in patients with germline mutations or deletions of ATM. Similarly, the approach to systematically inhibit ATM by pharmacological intervention has not shown clinical success because of the indiscriminating nature of radiosensitization. Somatic mutations of ATM have been suggested as an optimal prognostic marker of B-cell neoplasm (Guarini et al., 2012; Skowronska et al., 2012). In chronic lymphocytic leukemia (CLL), targeting the DNA damage repairing mechanism has been considered as a therapeutic option (Willmore et al., 2008). In MCL cell lines, the radiosensitvity appeared to be mediated by inactivation of the ATM gene, irradiation induced apoptosis and a major decrease in DNA-PKcs (M'Kacher et al., 2003). A reduction in the DNA-PKcs increases the possibility of spontaneous cytogenetic abnormality. Thus, cells with somatic ATM mutation can be targeted with radiation and pharmacological inhibition of the DNA-PK.

4. ATM mutation in mantle cell lymphoma

Mantle cell lymphoma (MCL) is a chemoresistant B-cell malignancy with the hallmark translocation t(11;14)(q13;q32). This translocation leads to over expression of cyclin D1 (CCND1) not found in normal B lymphocytes and results in a de-regulated cell cycle (Jares et al., 2012). While the CCND1 translocation is thought of as a primary oncogenic mechanism, multiple alterations in the epigenetic events and aberrant B-cell signaling pathways are also reported. Disruption of the DNA damage response pathways is one of the key contributors to the oncogenesis in MCL (Jares et al., 2007; Cheah et al., 2016). Through next generation sequencing techniques, an unprecedented number of scientific reports are now identifying genetic alterations in the MCL tumor cells from patients. We reviewed studies that profiled gene mutations in MCL and identified that ATM is the most frequently mutated gene among MCL (Table 1). Six studies profiled somatic mutation in tumor samples collected from 511 patients with MCL. Among the reported mutations, ATM was the most frequent recurrent mutations as identified by whole exome sequencing (WES) and targeted sequencing (RNA-seq). Overall, 239 of 511 (47%) patients harbored ATM mutation. It is important to note that the ATM mutation in MCL is of somatic origin that is acquired in the tumor cells; although germ line mutation of ATM may be a very infrequent finding (Fang et al., 2003). The majority of the studies reported deleterious missense point mutations, with or without 11q deletion (Bea et al., 2013; Greiner et al., 2006; Meissner et al., 2013; Rahal et al., 2014; Rossi et al., 2015; Zhang et al., 2014). The method of mutation analysis with types of mutation identified in MCL is summarized in Table 1. Given that about 47% of the MCL patients harbor ATM mutation, which renders cells radiosensitive, it is an attractive strategy to assess radiotherapy as a curative treatment option. However, it is crucial to address the issue of toxic response of normal cells to radiotherapy. That question may now be answered thanks to some very innovative experiments by Moding et al. as described in Section 6 below.

Treatment choices for MCL largely depend on the age and comorbidities that are present among patients. There are several treatment regimens available for induction therapy but controversy exists regarding frontline standard of care (Cheah et al., 2016). For relapsed and refractory patients, four novel agents received regulatory approval for treating MCL: bortezomib, temsirolimus,