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AUTHOR'S VIEW

ATM: An unexpected tumor-promoting factor in HER2-expressing tumors

Venturina Stagni[a], Veronica Oropallo[a,b], and Daniela Barilà[a,b]

[a]Laboratory of Cell Signaling, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Fondazione Santa Lucia, Rome, Italy; [b]Department of Biology, University of Rome "Tor Vergata", Rome, Italy

ABSTRACT
ATM kinase is a gatekeeper of genome stability. However, its role in several other signaling pathways suggests that it might not always act as a tumor suppressor. Here, we discuss recent data that unveil a function of ATM as a tumor promoter in HER2-positive breast cancer.

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Ataxia telangiectasia mutated (ATM) kinase is a key player of the DNA damage response (DDR) and its loss of function may lead to cancer development.[1] Interestingly, ATM activity has been also linked to signaling pathways that sustain tumor growth, thus raising the question of whether ATM might have a multifaceted role in cancer depending on the specific tumor context.[2]

In investigations into the role of ATM in the modulation of tumorigenicity dependent on the human epidermal growth factor receptor 2 (HER2, also known as v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 [ERBB2]) receptor tyrosine kinase (RTK), we provided the first experimental evidence for *ATM* as a tumor promoter gene.[3] *ATM* promotes the tumorigenicity of HER2-positive breast cancer cell lines *in vitro* and *in vivo*. This finding deserves some consideration. The first is that both genetic inhibition of ATM expression and pharmacologic inhibition of ATM kinase activity downregulate HER2 functionality (Fig. 1), supporting the idea that ATM sustains tumorigenicity by its ability to phosphorylate and modulate the function of some of its target proteins. The substrates of ATM in HER2 signaling have not yet been identified. Interestingly, based on our data, we can speculate that the ability of ATM to modulate HER2 is independent of the status (wild-type or mutated) of *p53* (TP53 best known as p53).

We described a positive feedback loop in which HER2 promotes ATM kinase activity and, conversely, ATM promotes HER2 expression. A major open issue regards the molecular mechanism by which HER2 promotes ATM activity either via the DNA damage response triggered by oncogenic stress and/or via oxidative stress associated with the aberrant activation of RTKs (reviewed in[4]).

We have provided evidence for ATM kinase activity as a promoter of HER2 protein stability *in vitro* and *in vivo*. ATM sustains the interaction between HER2 and heat shock protein 90 (HSP90), the principal modulator of HER2 protein stability, and its inhibition significantly reduces formation of the HER2-HSP90 complex, resulting in ubiquitination and degradation of HER2 [3] (Fig. 1). It will be important to clarify the subcellular localization of this complex and to uncover the mechanism through which ATM kinase activity modulates its assembly. Interestingly, HSP90 has been previously identified as a substrate of ATM in the DDR.[5] We speculate that ATM may trigger HSP90 phosphorylation downstream HER2: ATM might directly enhance the ability of HSP90 ability to interact with HER2 or might act indirectly by promoting the interaction of HSP90 with one of its co-chaperones. Our preliminary evidence suggests that ATM participates in a trimeric complex with HSP90 and HER2 (Fig. 1). Future experiments will clarify this issue.

The identification of ATM as a negative regulator of HER2 tumorigenicity was indeed unexpected and whether this is specific to the HER2 receptor or may be extended to other RTKs, or even in general to other tumorigenic contexts, is still obscure. Importantly, ATM can counteract HER2- but not RAS-dependent transformation. The main challenging questions are: (1) Does ATM activation represent a prognostic or therapeutic target? and (2) What are the tumorigenic contexts in which ATM expression/activity may confer a selective advantage to cancer cells?

Regarding the first question, the activation of ATM has been previously identified in several human tumors and described as a part of the DNA-damage response barrier to cancer development.[6] This hypothesis is supported by the detection of ATM activation already in early pre-invasive stages of tumor development together with the presence of markers of senescence and apoptosis. By investigating the correlation between ATM activation and the disease-free survival of patients with HER2-positive breast cancer who

CONTACT Daniela Barilà daniela.barila@unioma2.it

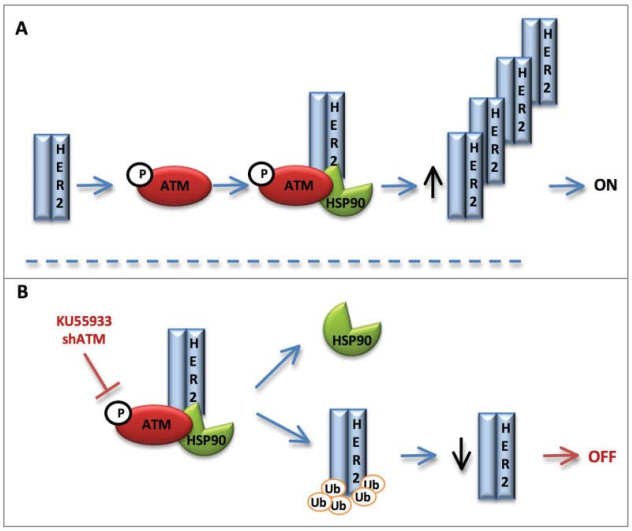

Figure 1. Role of ATM in HER2-dependent tumors. (A) ATM sustains HER2-dependent tumorigenicity (ON): HER2 triggers ATM activity, which supports HER2 complexation with HSP90. This results in an increase in HER2 protein levels (black arrow), which promotes tumorigenicity. (B) Genetic (shATM) or pharmacologic (KU-55933) inhibition of ATM expression or activity suppresses HER2-dependent tumorigenicity (OFF): ATM inhibition causes destabilization of the HER2-HSP90 complex and HER2 is subsequently ubiquitinated and degraded (black arrow).

were not treated with trastuzumab, we provided the first *in vivo* evidence that ATM activation might represent a prognostic marker to identify HER2-positive patients with the worst prognosis.[3]

We demonstrated that pharmacologic inhibition of ATM by KU-55933 injection inhibits tumor growth *in vivo* in a transgenic mouse model expressing rat HER-2/neu oncogene in the mammary gland.[3] This observation opens the way to pharmacologic modulation of ATM activity *in vivo* to delay tumor growth, at least in particular contexts.

Although ATM inhibitors suitable for clinical trials are still lacking, inhibition of ATM activity has been investigated as a valuable approach to sensitize tumors to radiotherapy and chemotherapy.[7] We believe that the landscape of therapeutic settings that may benefit from ATM inhibition is expected to grow. ATM inhibition may also be beneficial for modulation of HER2 activity, and for the response to trastuzumab and tamoxifen. Interestingly, HER2 contributes to the maintenance of breast cancer stem-like cells, which are responsible for both the onset and the relapse of the tumor.[8] Therefore, it is intriguing to postulate that ATM inhibition represents a valuable therapeutic tool to target these cells.

Regarding the second question, it is worth discussing two recent studies. The identification of a functional interplay between ATM and alternative reading frame (ARF) tumor suppressor protein revealed that ATM inhibition promotes ARF induction and may therefore be a valuable tool to block tumor progression, particularly in tumors with non-functional p53.[9] More recent studies using a melanoma model elegantly identified a significant contribution of ATM to hypoxia-induced angiogenesis and tumor expansion, pointing to ATM inhibition as a tool to trigger synthetic lethality in hypoxic conditions.[10]

In summary, the identification of a tumorigenic role of ATM in HER2 tumor progression provides a proof of concept for a dual role of ATM activity in cancer and strongly supports the requirement for additional studies to validate its prognostic and therapeutic significance.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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