

# Chronic activation of DNA damage signals causes tumor immune evasion in the chemoresistant niche

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**Keywords:** DNA damage response, ATM, NFκB, integrin-αvβ3, tumor immunity

**Abbreviations:** ATM, ataxia telangiectasia mutated; NFκB, nuclear factor-kappaB; NKG2D, natural killer gene complex group 2 member D; chk-2, checkpoint kinase-2; DC, dendritic cells

DNA damage responses have been proposed as a gatekeeper to block tumorigenesis. We identify unexpected mechanisms whereby ATM-mediated pathway interacts with NFκB inflammatory cascades, leading to upregulation of integrin-αvβ3 on chemoresistant tumor cells. The integrin-αvβ3 is responsible for impeding tumor-specific immune responses, linking chemoresistant niche with tumor immune evasion.

DNA damage checkpoint machineries serve as a gatekeeper to keep cellular and genetic integrity at steady-state. The activation of DNA damage repairing systems is frequently detected in pre-cancerous and early tumor lesion, leading to cell cycle arrest and apoptosis by p53-dependent mechanisms.<sup>1</sup> In addition of their direct actions to cell-intrinsic DNA replication stress, DNA damage pathways are responsible for inducing NKG2D ligands on stressed cells, and activate innate immune lymphocytes such as NK cells and γδT cells to eliminate cells in which accumulation of excessive genetic damage may lead to oncogene activation and transformation.<sup>2</sup> Moreover, the activation of DNA damage signals causes proinflammatory cytokine secretion from senescent tumor cells, further amplifying antitumor innate immune responses against transformed cells.<sup>3,4</sup> Thus, DNA damage responses have critical functions in maintaining cellular and genetic homeostasis by coordinately regulating genetic and environmental sensing systems. However, continuous activation of DNA damage signals, which is frequently occurred during tumor progression, may

contribute to genomic instability and selective pressure to trigger p53 mutation, leading to disruption of cell cycle arrest and apoptosis. Thus, oncogene-induced activation of DNA damage signals may mediate diverse array of biological consequences, which is dependent on distinct sets of signals and their downstream mediators delivered by various micro-environment.

Recent evidences have unveiled the role of tumor cells in the regulation of the biologic properties of stromal cells, endothelial cells, and host immunity in local microenvironments, leading to further tumor progression and a worse prognosis.<sup>5,6</sup> Therefore, the acquisition of anticancer drug resistance may render tumor cells with the ability to modulate their microenvironments in a paracrine fashion, further enhancing survival signals and the progression of tumors. However, the molecular mechanisms regulating interplay between tumor cells and immune cells to create chemoresistant microenvironments remain largely obscure.

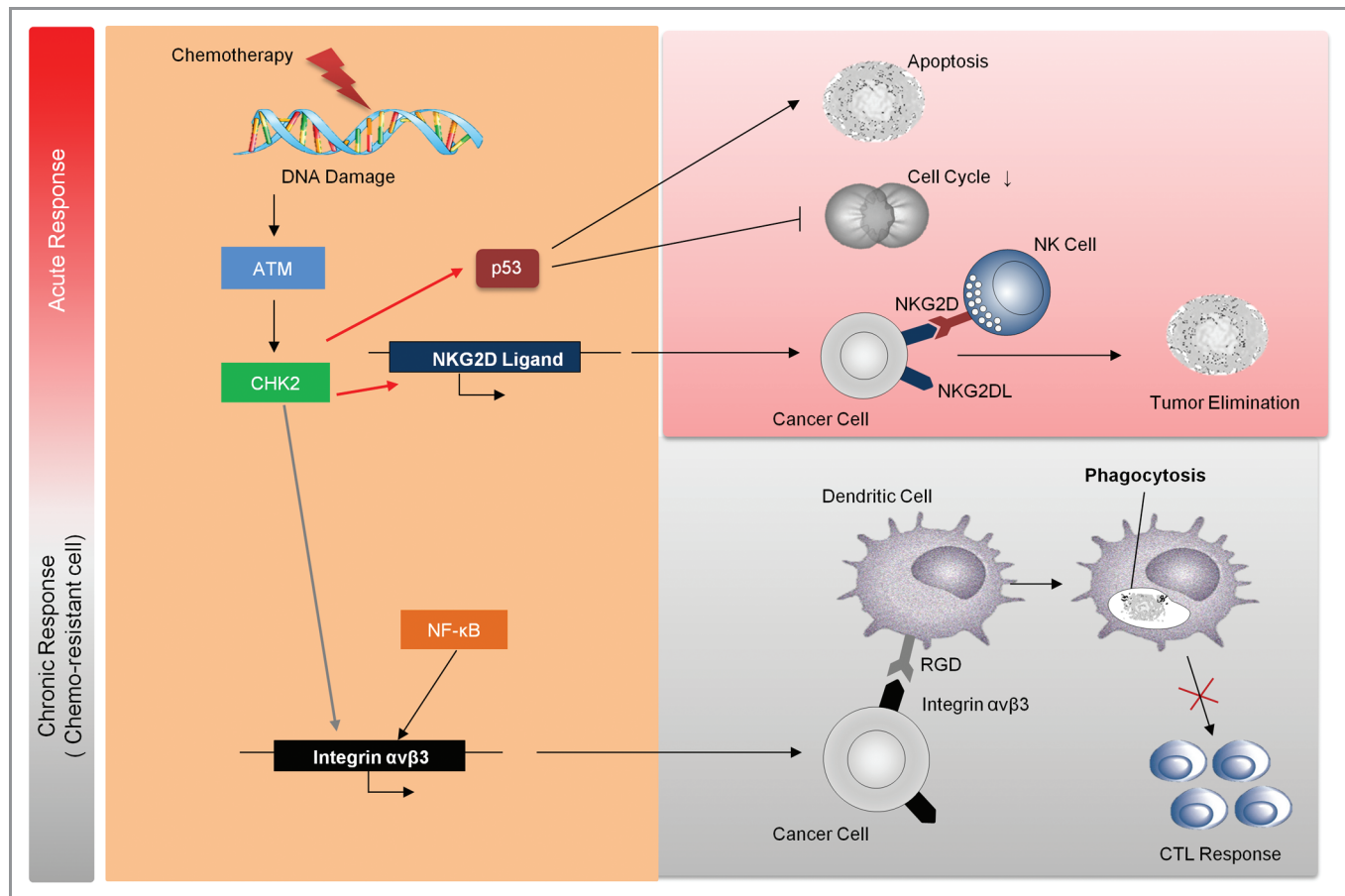
We recently found some unexpected aspects of DNA damage signals on anti-cancer drug resistance of tumor cells. The

tumor cells acquired resistance to various chemotherapeutic drugs exhibit constitutive activation of sets of DNA damage signals, ATM and chk-2. The constitutive activation of ATM-mediated activation of DNA damage pathways is indispensable for triggering integrin-αvβ3 induction on tumor cells. Furthermore, integrin-αvβ3 on tumor cells facilitate the uptake of viable tumor cells by dendritic cells in RGD-dependent manner, by which cross-presentation of immunogenic antigens and induction of tumor-specific cytotoxic T lymphocytes are severely compromised at tumor microenvironments.<sup>7</sup>

Overall, these findings provide novel mechanistic insights whereby cell intrinsic and environmental regulation of therapeutic responses may change the genetic profiles of tumor cells to activate distinct sets of DNA damage pathways, causing the induction of downstream mediators responsible for modulating tumor microenvironments and supporting further tumor progression by compromising endogenous host immunity.

Although the molecular machineries that ATM-mediated DNA damage responses cause integrin-αvβ3 upregulation

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**Figure 1.** The dynamics of DNA damage responses in the regulation of tumorigenicity and antitumor immune responses. The activation of DNA damage pathways has an important role in eliminating tumor cells with excessive DNA replication stresses through coordinated activation of p53 in damaged cell and NKG2D-dependent innate immune responses. However, under the circumstances where tumor cells are chronically exposed to genotoxic stress and inflammatory environments, constitutive activation of ATM and NFκB renders tumor cells with the ability to downregulate antitumor immunosurveillance in part through upregulation of integrin- $\alpha v \beta 3$  on tumor cells and impairment of DC-mediated induction of antitumor CTL.

remain unresolved issue, unique genotoxic stress-induced systems mediated by ATM-dependent DNA damage signals and NF- $\kappa$ B-mediated inflammatory cascades, are required for inducing integrin- $\alpha v \beta 3$  on therapy-resistant tumor cells.<sup>7</sup> Consistent with these findings, previous study unveiled novel pathways in which ATM stimulates NFκB-mediated inflammatory signals in response to genotoxic stimuli such as cytotoxic drugs and irradiation.<sup>8</sup> Although Ashkenazi et al. recently suggested that acute phase of DNA damage signals could increase the susceptibility to apoptotic cell death of HeLa cells through NEMO and TNF $\alpha$ -mediated pathways,<sup>9</sup> the same pathways may in turn contribute

to increased cell survival when chemoresistant tumor cells manifest constitutive activation of ATM and NFκB. Since NFκB has been established as a critical sentinel linking inflammation with carcinogenic process,<sup>10</sup> chronic activation of DNA damage responses in tumor cells may be linked with inflammation-associated carcinogenesis. Moreover, the continuous activation of ATM and NFκB in chemoresistant tumors may be linked with induction of downstream effectors responsible for modifying tumor microenvironments such as integrin- $\alpha v \beta 3$ , and promoting tumorigenic and metastatic potential. In these perspectives, we propose the novel pathways whereby chronic

activation of ATM and NFκB renders tumor cells with the ability to downregulate antitumor immunosurveillance, at least in part through upregulation of integrin- $\alpha v \beta 3$  on tumor cells. In contrast, acute responses of DNA damage efficiently eliminate excessively damaged cells by activating p53-dependent pathways and antitumor innate immune responses (Fig. 1).

Further elucidation and deep understanding of mechanisms linking DNA damage signals with inflammatory cascades and their impact on tumor microenvironments should explore new strategy to target tumors refractory to current anti-cancer regimens.

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