TP53 genomic status regulates gastric cancer cell fate decision in response to EZH2 inhibition

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As a polycomb protein methyltransferase, Enhancer of zeste homolog 2 (EZH2) plays a pivotal role in epigenetic silencing. Mechanistically, the oncogenic function of EZH2 has been assigned to associated histone H3 with trimethylated lysine 27 (H3K27me3), leading to transcriptional repression of tumor suppressor genes. As one of its targets, p53/p21 pathway is also well known to be critical in determining cellular sensitivity to DNA damaging agents. Using gastric cancer cells with different TP53 genomic status, we explore that EZH2 depletion not only works in coordination with DNA damage caused by Doxorubicin (DOX) in progression of cellular senescence but also apoptosis in mutant type cells. However, there is no synergistic effect in wild type cells. These results reveal the vital role of EZH2 in senescence and apoptosis progress and that TP53 genomic status have influence on cellular responses to EZH2 depletion in gastric cancer cells.

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Enhancer of zeste homolog 2 (EZH2) as one of the first protein lysine methylase involved in cancers, is over-expression in many kinds of human cancers, having an important effect on tumors proliferation, metastasis and senescence [1, 2], which has been considered a promising potential target in cancer therapy. It specially trimethylates lysine 27 of histone H3 (H3K27me3) through the SET domain, thus regulates genes expression via epigenetic regulatory manner [3, 4]. p53/p21 pathway is one of them[5]. Doxorubicin (DOX) as a member of chemotherapeutic drugs, is known to induce senescence by DNA damage response [6] at a concentration significantly lower than it required for induction of apoptosis[7], and this progression is dependent on the slight activation of p53/p21 pathway[8]. Above observations raise our interests to identify the consequence of EZH2 silencing with low concentration of DOX and mechanisms involved in gastric cancer cell lines.

In our recent studies, we treated gastric cancer cells with low concentrations of DOX and found that most cells, whatever the genetic status of TP53 is, showed enlarged and flattened morphology, senescence-associated-β-galactosidase (SA-β-gal) activity, senescence-associated heterochromatic foci (SAHF) and cell cycle arrested [9]. Above-mentioned changes of cellular morphology and mitotic activity approved that low doses of DOX could induce senescence efficiently in gastric cancer cells by slight DNA damage responses.

Then we observed that EZH2 down-regulation could inhibit cellular proliferation of gastric cancer cells and this
outcome was more significant in coordination with DOX. Mechanistically, EZH2 silencing caused senescence and apoptosis in p53 mutant type, but just increase of proportion of apoptosis in p53 wild type cancer cells. Under the co-treatment of EZH2 depletion and DOX, cellular senescence and apoptosis were more profound in cells with mutant p53, however, there was little synergistic effect in wild type cells [9]. The interesting results motivated us to explore relationships between TP53 genomic status and different cellular responses.

Apoptosis and senescence are diverse causes to cancer suppression [10, 11] and share p53/p21 regulatory pathway [5]. As a central player in tumor suppression and therapy, p53’s ability to suppress tumorigenesis in human has been extensively researched [12]. It is viewed as a key factor in tumor suppression. Given p53’s central position in the responses to stress stimuli, the decision between senescence, apoptosis and growth arrest is thought to be determined by appropriate expression level of p53 [13]. The qualitative status of p53 may be decisive for different cellular responses: higher levels induce apoptosis, while low levels of p53 favor growth arrest.

In p53 mutant type cancer cells MKN28, DOX or EZH2 inhibitor could increase the level of p53 slightly then induce cells to senescence. When both of them are present, p53/p21 pathway is further activated but remains at low level, which causes senescence more significant. On the other hand, either EZH2 inhibitor or DOX could activate p53/p21 pathway in wild type. Low-dose of DOX causes p53 activated slightly, thus results in senescence. EZH2 inhibitors activate p53 gene to a high expression level, inducing apoptosis, which is the most striking characteristic in AGS after EZH2 down-regulated [9]. Consistent with our results, Wu [14] has reported that inhibition of EZH2 leads abolishment of both G1 and G2/M checkpoints, promoting DNA damage response towards apoptosis in both p53 wild type and p53-deficient cancer cells.

Together, our studies on the outcome of gastric cancer cells under the treatment of EZH2 inhibitor combined with DOX and involved mechanisms reveal an important role of EZH2 in senescence and apoptosis in gastric cancer cells, and that p53 status could determine the cellular responses to EZH2 depletion. Given the side effect of chemotherapy, any method that could sensitize cancer cells to even a slight DNA damage and result in senescence or apoptotic, would have the value to be paid great attention. Although the different responses, EZH2 depletion could promote the ability of anti-proliferation by low doses of DOX, no matter p53’s status. We could regard it as a sensitizer which not only enhances the capability of DNA damaging chemotherapeutic reagents and but also reduces the side effects. In conclusion, we showed that the combined treatment of EZH2 inhibitors and low doses DOX may be a beneficial therapy for a subset of gastric cancer patients.

**Conflicting interests**

The authors have declared that no competing interests exist.

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