Breast Cancer RESEARCH

VIEWPOINT

Chemosensitivity and p53; new tricks by an old dog

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Abstract

The effect of *TP53* mutations on chemosensitivity in breast cancer is a controversial issue. In an elegant paper in *Cancer Cell*, Jackson and colleagues report wtp53 protein to block anti-tumour effects of doxorubicin treatment in mice. p53 did so by inducing senescence, thereby preventing mitotic catastrophy and subsequent cell death. In contrast, while *TP53* mutations have shown to predict response to cyclophosphamide high dose therapy, mutations in general have been associated with anthracycline resistance in human breast cancers. The challenging results from Jackson and colleagues' study elucidate a new hypothesis and suggest directions for future translational research in human breast cancer.

Few genes have been more extensively studied in cancer biology than *TP53*, the gene coding for the p53 protein. p53 is involved in multiple cellular processes, including growth arrest, senescence, apoptosis and DNA repair; recent evidence has also added necrosis to the list [1]. Its role as a tumour suppressor is well confirmed and patients harbouring germline *TP53* mutations suffer a high risk of early cancers. Regarding somatic events, *TP53* is the single gene most frequently mutated in malignant conditions, with an incidence rate of 25 to 30% in breast cancers. *TP53* mutations have been associated with poor prognosis and, more controversially, with chemosensitivity.

A recent paper by Jackson and colleagues [2] adds interesting information on this topic. In an elegant study using a MMTV-*WNT1* mouse mammary tumour model, they generated $p53^{R172H}$ (corresponding to the deleterious human codon 175 mutation), $p53^{-/-}$ and $p21^{-/-}$ mice. As expected, mice carrying homozygous p53 mutations/deletions had shorter tumour latency compared to wild-type mice. Treating animals with established tumours with intraperitoneal doxorubicin (4 mg/kg body weight), they found *TP53* mutated tumours to undergo mitotic catastrophe with subsequent cellular death and tumour shrinkage. In contrast, wt*TP53* tumours responded to doxorubicin treatment by senescence, lack of tumour shrinkage, and more rapid re-growth. Interestingly, $p21^{-/-}$ tumours revealed an intermediate response; some, but not all, responding by growth arrest. So, what may be the relevance of these findings to human cancers and clinical research?

Clinical data on the predictive role of *TP53* mutations for drug resistance versus sensitivity are limited, and we should be aware of their limitations. p53 immunostaining is a poor surrogate marker for *TP53* mutation status since 25 to 30% of all *TP53* mutations in breast cancer (nonsense mutations associated with drug resistance in particular) do not reveal elevated immunostaining [3]. Taking patients treated with either an anthracycline monotherapy, anthracycline with cyclophosphamide at regular doses or mitomycin regimen, four studies have revealed inferior responses in *TP53*-mutated tumours [3-6]. Two studies [4,7] found no effect of *TP53* mutation status on response to taxanes. In contrast, de Thé and colleagues [8] reported *TP53* mutations to be associated with increased chance of having a complete response. Importantly, in their studies they applied a regimen providing epirubicin (75 mg/m^2) and a high dose of cyclophosphamide (1,200 mg/m^2) at 2-weekly intervals. Including two additional series of patients treated with either epirubicin monotherapy or a FEC (5-fluorouracil, epirubicin and cyclophosphamide) regimen at regular doses, they confirmed the predictive value of *TP53* mutations to pathological complete response was related to dose-dense administration of cyclophosphamide [8]. While conflicting results from human studies may be related to drug regimens applied, it is noteworthy that Jackson and colleagues [2] applied doxorubicin monotherapy at a dose commonly used for such experiments in mice.

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In addition to the findings in *TP53* itself [3-6], indirect evidence also supports the hypothesis that lack of p53 function may cause drug resistance. Recent studies by our group have linked *CHEK2* mutations as well as low ATM-expression (the two most important p53 activators in response to DNA damage [9]) to anthracycline resistance in primary breast cancers harbouring wt*TP53* [6,10].

Importantly, senescence, and probably apoptosis as well, does not occur through activation of just a single gene pathway. Thus, Schmitt and colleagues [11] confirmed senescence activated by the concerted action of the p16/retinoblastoma and p53 pathways to cause tumour regression in response to cyclophosphamide treatment in a mouse lymphoma model. Similar mechanisms may be operating in human tumours; we detected inactivating mutations in the retinoblastoma gene to be associated with resistance toward low-dose anthracycline or mitomycin therapy in primary breast cancers [12].

Our knowledge about the complexity of p53 function is growing [13], and the recent study by Jackson and colleagues [2], together with some other recent remarkable studies [14,15], indicates that the mechanism of tumour suppression and response to acute DNA damage may be, at least partly, different. Jackson and colleagues' study clearly underlines the need for more sophisticated studies to elucidate the potential role of *TP53* status to drug sensitivity in human cancers, bearing in mind potential differences between mice and humans. Further, apart from *TP53* mutation status, we need to examine interacting factors; while Jackson and colleagues point to the importance of concomitant *TP53* loss of heterozygosity, available human data (although limited) have not defined this as a discriminator [3]. Other factors include p53 splice variants. While p53γ co-expression has been shown to neutralize the poor prognostic impact of *TP53* mutations [16], its effect on chemosensitivity, however, remains to be explored. In addition, we need to assess mutations affecting genes acting up/downstream of p53 as well as genes involved in redundant pathways. Most importantly, whenever possible we should collect tissue samples post-chemotherapy to address whether the findings by Jackson and colleagues in their mouse model could be reproduced in humans and correlate potential findings to *TP53* status, anti-tumour response and long-term survival.

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Competing interests
The authors declare that they have no competing interests.

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