Commentary

Some aspects of mutant p53 in ovarian cancer biology

Sabine Heublein

Department of Gynaecology and Obstetrics, National Center for Tumor Diseases (NCT), University Hospital Heidelberg, Heidelberg, Germany
Correspondence to: Sabine Heublein, MD, PhD. Department of Gynaecology and Obstetrics, National Center for Tumor Diseases (NCT), University Hospital Heidelberg, Im Neuenheimer Feld 440, 69120 Heidelberg, Germany. Email: sabine.heublein@med.uni-heidelberg.de.
Comment on: Ren YA, Mullany LK, Liu Z, *et al*. Mutant p53 Promotes Epithelial Ovarian Cancer by Regulating Tumor Differentiation, Metastasis, and Responsiveness to Steroid Hormones. Cancer Res 2016;76:2206-18.

Submitted Jul 27, 2016. Accepted for publication Aug 08, 2016.
doi: 10.21037/tcr.2016.09.21
View this article at: http://dx.doi.org/10.21037/tcr.2016.09.21

Epithelial ovarian cancer (EOC) is known as the most lethal gynaecologic malignancy. The poor prognosis of EOC has been attributed to e.g., late diagnosis of the disease and to chemoresistance. Further, we are still missing biomarkers that may reliably predict prognosis or chemosensitivity of an individual patient.

Mutations of *TP53*, which encodes the tumour suppressor protein p53, seem to be present in the large majority of serous ovarian cancer cases and are supposed to majorly influence pleiotropic tumour-biologic characteristics of EOC (1). For instance, since p53 plays a critical role in apoptosis and proliferation, loss of active p53 is closely associated with multidrug resistance (2). Intriguingly, unlike other 'classical' tumour suppressor genes mutations in *TP53* comprise some special features contributing to a complex tumour-biologic phenotype. First, while 'classical' tumour suppressor genes (TSGs) commonly undergo mutations that cause either deletion or truncation of the gene product, most of the aberrations detected in *TP53* are single base substitutions that cause hyper-stabilization of p53 (3). Second, though wild-type p53 is known as a tumour suppressor, some mutations in *TP53* may actively drive oncogenesis by activating tumour promoting processes. Those aberrations that are able to promote tumorigenesis may—due to historical reasons—be termed 'gain-of-function' mutations, since oncogenic activities are 'gained' while tumour suppressive features are 'lost' (3). Third, some mutations in *TP53* may exert dominant negative effects on the wild type allele (4,5).

Numerous studies investigated a potential prognostic or predictive use of mutant *TP53*. However, the results reported in these trials are conflicting. This may at least partly be due to the different methods employed thus to detect *TP53* mutations and to the fact that there is no consent on how to group *TP53* mutations that may exert distinct biological effects. A comprehensive review by Brachova *et al.* defined four types of *TP53* mutations: wild type, loss of wild type function, partial loss of wild type function, and gain of function (so called 'oncomorphic') (3). Whether sub-grouping of mutations as suggested by Brachova *et al.* may help to elucidate clinical use of *TP53* aberrations remains to be determined.

A recent work by Ren *et al.* published in Cancer Research dissected tumour-biological effects of such an—most likely—'oncomorphic' mutation in *TP53* (5). The authors were able to demonstrate that *Trp53R172H* holds oncogene-like activity and—even more interesting—exerts different biological effects depending on whether the wild type allele was expressed or not. Mice carrying both the wild type and the mutant (*Trp53R172H*) allele at the same time presented with marked peritoneal carcinomatosis. Furthermore, their tumours showed strong stromal invasion and high expression of *ESR1* encoding estrogen receptor alpha. Importantly, heterozygous tumours retained responsiveness to p53 activating nutilin-3a. Most interestingly, those mice heterozygous for *Trp53R172H* developed a type of EOC closely resembling the mucinous subtype in humans. Having excluded mucinous ovarian neoplasms of low malignant potential and cases diagnosed with metastasis originally deriving from gastro-intestinal malignancies, mucinous ovarian carcinomas account for less than five percent of EOC (6-8). Mucinous EOC cases display some distinct clinical and biological characteristics. Though patients diagnosed with mucinous EOC staged as FIGO I have rather good prognosis, both OS and PFS of those women diagnosed with mucinous EOC classified as FIGO III are even shorter than in staged matched patients with serous EOC (8,9). This may be attributed

to the high frequency of platinum resistance found in mucinous EOC (10). Accordingly, *TP53R172H* among other gain of function mutations has been demonstrated to be associated with platinum resistance (11). Whether re-activation of remaining p53 function by nutilin-3a may add to overcome platinum resistance in a model of mucinous ovarian cancer needs to be determined. Those tumours homozygously expressing *Trp53R172H* displayed a distinct molecular profile that was markedly different from those of heterozygous counterparts. Moreover, complete loss of the wildtype allele was associated with highly metastatic potential, low histologic differentiation, and with poor transactivation activity.

Altogether, Ren *et al.* revealed several novel aspects on biological activity of a *TP53* gain of function mutation that may turn out to be of clinical relevance in the future. Further studies on *TP53R172H* (human homolog of mice *Trp53R172H*) in human ovarian cancer cases need to be performed thus to further elucidate its clinical utility.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Da Li (Department of Obstetrics and Gynecology, Shengjing Hospital of China Medical University, Shenyang, China).

Conflicts of Interest: The author has completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.09.21). The author has no conflicts of interest to declare.

Ethical Statement: The author is accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Cancer Genome Atlas Research Network. Integrated genomic analyses of ovarian carcinoma. Nature 2011;474:609-15.
2. Fraser M, Bai T, Tsang BK. Akt promotes cisplatin resistance in human ovarian cancer cells through inhibition of p53 phosphorylation and nuclear function. Int J Cancer 2008;122:534-46.
3. Brachova P, Thiel KW, Leslie KK. The consequence of oncomorphic TP53 mutations in ovarian cancer. Int J Mol Sci 2013;14:19257-75.
4. Willis A, Jung EJ, Wakefield T, et al. Mutant p53 exerts a dominant negative effect by preventing wild-type p53 from binding to the promoter of its target genes. Oncogene 2004;23:2330-8.
5. Ren YA, Mullany LK, Liu Z, et al. Mutant p53 Promotes Epithelial Ovarian Cancer by Regulating Tumor Differentiation, Metastasis, and Responsiveness to Steroid Hormones. Cancer Res 2016;76:2206-18.
6. Shimada M, Kigawa J, Ohishi Y, et al. Clinicopathological characteristics of mucinous adenocarcinoma of the ovary. Gynecol Oncol 2009;113:331-4.
7. Seidman JD, Kurman RJ, Ronnett BM. Primary and metastatic mucinous adenocarcinomas in the ovaries: incidence in routine practice with a new approach to improve intraoperative diagnosis. Am J Surg Pathol 2003;27:985-93.
8. Brown J, Frumovitz M. Mucinous tumors of the ovary: current thoughts on diagnosis and management. Curr Oncol Rep 2014;16:389.
9. Winter WE 3rd, Maxwell GL, Tian C, et al. Prognostic factors for stage III epithelial ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2007;25:3621-7.
10. Pignata S, Ferrandina G, Scarfone G, et al. Activity of chemotherapy in mucinous ovarian cancer with a recurrence free interval of more than 6 months: results from the SOCRATES retrospective study. BMC Cancer 2008;8:252.
11. Kang HJ, Chun SM, Kim KR, et al. Clinical relevance of gain-of-function mutations of p53 in high-grade serous ovarian carcinoma. PLoS One 2013;8:e72609.

Cite this article as: Heublein S. Some aspects of mutant p53 in ovarian cancer biology. Transl Cancer Res 2016;5(S3):S546-S547. doi: 10.21037/tcr.2016.09.21