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LETTER TO THE EDITOR, NEWS AND VIEWS

Opinion letter regarding the article *Arch Toxicol* https://doi.org/10.1007/s00204-018-2240-x

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The article *Sensitization of colorectal cancer cells to irinotecan by the Survivin inhibitor LLP3 depends on XAF1 proficiency in the context of mutated p53* written by Maja T. Tomicic and colleagues, recently published in *Archives of Toxicology*, brought to my mind once again the importance of molecular profiling of tumour; personalised approach to each patient and deep diagnostic of tumour before the therapy has been applied. This article is showing very clearly how despite a huge knowledge we are already having about the colorectal cancer we still do not know all biomarkers, important signature molecules responsible for tumour behaviour, or what a final outcome of tumour therapy will be achieved. Our goal is to grasp all biomarkers, signalling pathways, their combinations, and switch-on/switch-off schedules of paths' activity. This knowledge will enable us to be a step ahead of tumour and be able to finally have a kind of book of tumour behaviour prediction—the collection of thousands of possible paths which tumour might take in a specific situation to survive counteracting therapy.

It is known that the majority of colorectal cancers (CRC) develop via a chromosomal instability pathway. Approximately 12–15% of CRC show deficiency in the mismatch repair (dMMR), which is characterized by microsatellite instability (MSI). Tumours with the dMMR/MSI develop from a germline mutation in one of the MMR genes (*MSH2, MSH6, MLH1, PMS2*), i.e., Lynch syndrome, or more commonly from epigenetic inactivation of *MLH1*. Consistent data indicate that these tumours have a better stage-adjusted survival, as compared to proficient MMR or microsatellite stable tumours, and may respond differently to 5-fluorouracil-based adjuvant chemotherapy (FOLFOX/FOLFIRI) (Curr Treat Options Oncol. 2015; 16:30; Fam Cancer. 2016; 15:405–412).

This article is emphasising the importance of knowing the p53 status of CRC cells, showing that therapy based on targeting inhibitors of apoptosis (IAP), using specific direct inhibitors, here particularly the direct Survivin inhibitor LLP3, could be effective as mono-therapy in p53-proficient and some p53-mutated CRC, in fact independently of the MMR status. Moreover, if the conventional therapy such as FOLFIRI, containing irinotecan, in combination with LLP3 is administered, then the XAF1 and the p53 status need to be determined. It will be interesting to see the confirmation of these data in vivo. Moreover, it will be also interesting to see whether tumour cells of different origin but the similar genetic landscape will respond to the therapy the same. The personalised oncology is already a movement which is promoting therapy tailoring according to molecular profiling, not the tumour tissue origin. Recent, FDA-approved humanized antibody against the programmed cell death 1 (PD-1) receptor (pembrolizumab) is good evidence in which direction we are moving. This is the first time that the agency has approved a cancer treatment based on a common biomarker rather than on the tumour origin.

The fact that IAPs are involved in so many important cell functions such as direct prevention of apoptosis, regulation of cell shape, migration and tumour metastasis, pro- and anti-migratory roles depending on the cellular context, and that they can regulate the plasticity of tumour cell migration plus the fact that they have been correlated to both negative and positive tumour prognosis make them important and feasible therapeutic targets (Cell Death Dis. 2013; 4:e784). Therefore, I look forward to reading more articles like this one and to attestation of the data in clinical setting.

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