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LETTER TO THE EDITOR

Why is p53-inducible gene 3 rarely affected in cancer?

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Dear Sir,

We read with great interest the work on the contribution of the p53-inducible gene 3 (*PIG3*) to the early cellular response to DNA damage (Lee *et al*., 2010). *PIG3* was considered until now as a p53-dependent proapoptotic gene mediating reactive oxygen species (ROS) production. p53 regulates *PIG3* through a polymorphic pentanucleotide sequence. An individual's constitution or deregulation of this repetitive sequence, by microsatellite instability (MSI), was postulated as potential mechanisms for cancer susceptibility (Contente *et al*., 2002). Collectively, we and others (Gorgoulis *et al*., 2004 and references therein), along with our additional unpublished data from 114 lung tumors (7% loss of heterozygosity (LOH) and 0.9% MSI), have shown that MSI and LOH rarely affect this locus in various common tumors, whereas rare pentanucleotide alleles are not associated with cancer risk. An alternative splicing of *PIG3* mRNA resulting in an unstable truncated variant (Nicholls *et al*., 2004) could represent another *PIG3* inactivation mechanism. Nevertheless, our unpublished work in a subset of the previously mentioned lung tumors for potential *PIG3* alternative splicing deregulation favoring the truncated form was not found. On contrary, the full-length transcript was predominantly found to be increased in tumor counterparts (96.7%). Collectively, these results raise the question: why is *PIG3* rarely affected in cancer?

Lee *et al*. (2010) provide new insights into the role of PIG3 and potentially the answer to the above question. Its presence in the nucleus, in which it functions as an upstream component of the DNA damage response (DDR) pathway, suggests that like other components, similarly located in this pathway, it must be intact. Upstream DDR components are rarely altered, in contrast to p53, as cancer cells are likely to rely on them to optimize the survival (Negrini *et al*., 2010 and references therein). Even more, p53 also regulates *PIG3* expression thus creating a potential positive feedback with the upstream DDR mechanism, suggesting that in the case of DNA damage p53 can also amplify directly the upstream response in normal cells. This may be valid for tumor cells also, given that certain p53 mutants activate *PIG3*, whereas the result of our study show increased full-length transcript expression in tumor counterparts. Therefore, p53 inactivation, as frequently seen in most types of tumors, is sufficient to 'compromise' this pathway, with the upstream components remaining intact as they may be vital for tumor cells. Finally, the cytoplasmic role of PIG3 as an ROS producer must not be altered also, as it may be involved in hypoxia-mediated tumor clone selection, as previously proposed (Gorgoulis *et al*., 2004).

Conflict of interest

The authors declare no conflict of interest.

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