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David F. Callen

p53 continues to surprise: High levels of p53 can suppress apoptosis

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p53 continues to surprise: High levels of p53 can suppress apoptosis

Comment on: Chee JLY, et al. *Cell Cycle* 2013; 12:278–88; PMID:23255126; <http://dx.doi.org/10.4161/cc.23054>

David F. Callen; Centre for Personalised Cancer Medicine; Faculty of Health Sciences; University of Adelaide; Adelaide, SA Australia; Email: david.callen@adelaide.edu.au; <http://dx.doi.org/10.4161/cc.23420>

On average, p53 is mutated in 50% of tumors. As results accumulate from large-scale cancer genome sequencing approaches, it is evident that underlying this average, p53 mutation rates in different tumor subtypes are highly heterogeneous. For example, p53 is mutated in over 80% of triple-negative basal-like breast cancers and 90% of high-grade serous ovarian cancers, while, in contrast, luminal A breast tumors are 88% wild-type p53.¹ These findings suggest that the tissue-specific genetic background of the precursor cancer cell can influence the subsequent route of p53 inactivation.

Missense mutations of p53 are common. These are frequently situated in the DNA binding domain of p53 (hotspot mutations), resulting in impairment of the ability of p53 to transactivate its downstream pathways. Such mutations not only obviolate the normal functions of p53, but also result in a gain of function, a focus of current research. This gain of function is associated with mutant p53 promiscuously cooperating with other transcription factors (for example, NF- κ B, VDR³ and p63⁴) resulting in expression of genes driving metastasis.

In the 50% of tumors with wild-type p53, how are the normal responses of p53 attenuated? There are presumably upstream, downstream or a combination of factors that suppress the normal critical damage sensor roles of p53. The nature of the sensors and responses when oncogenes are overexpressed are presently being unravelled.⁵ Normal cells maintain low levels of p53 protein to prevent the activation of the downstream apoptotic and other tumor suppressor pathways.

Unexpectedly, high levels of wild-type p53 protein are found in some tumors and are associated with metastasis and poor prognosis. The cancer cell can function in the face of these high levels of wild-type p53 by excluding the protein from the nucleus and relocating to the cytoplasm (e.g., ref. 6), thus limiting the transactivation of p53 target genes. Cancer cells with mutant p53 can also show high levels of the protein located in the cytoplasm. Since transactivation activity of mutant p53 is absent, this prompted Chee et al.⁷ to speculate that high levels of cytoplasmic p53 (wild-type or mutant) provide a gain of function and therefore a selective advantage to the cancer cell. The paper by Chee et al. provides compelling evidence that this gain of function results in increased resistance of the tumor cell to chemotherapeutic drugs.

In their study, Chee et al. showed that p53 can interact with and inhibit caspase-9, one of the critical caspases in the classical apoptosis cascade. At first this appears counter intuitive as one of the major transactivation pathways of p53 targets is to drive apoptosis in response to external or internal cellular stress. However, when the unusual cytoplasmic localization of the p53 in these cancer cells is considered, this begins to make sense. Increased resistance to cisplatin, a commonly used chemotherapeutic agent, is shown to be dependent on mutant or wild-type p53. One of their approaches utilizes an ecdysone-inducible system for expression of wild-type and mutant p53 in a p53-null H1299 cancer cell. This is a particularly powerful approach due to the lack of leaky expression often seen in other inducible

expression systems. The levels of either wild-type or mutant p53 correlate with increasingly specific inhibition of caspase-9. In normal cells the interaction of caspase 9 and p53 in the cytoplasm cannot be detected as p53 is preferentially located in the nucleus.

Therefore in tumor cells the consequences of high levels of cytoplasmic p53 are a possible mechanism to circumvent the expected toxic consequences of p53 but in addition a gain of function that imparts resistance to chemotherapeutic agents. These findings highlight the amazing plasticity of p53 and its exploitation by tumor cells to positively drive their survival pathways.

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