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OCT4A and the DNA damage response

Comment on: Huna A, et al. Role of stress-activated OCT4A in the cell fate decisions of embryonal carcinoma cells treated with etoposide. Cell Cycle 2015; 14(18):2980-95; PMID:26102294; http://dx.doi.org/10.1080/15384101.2015.1056948

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OCT4A is best known as a "master" transcription factor involved in stem cell pluripotency and self renewal in concert with SOX2 and NANOG. Although there has been some indication of a dialog between OCT4 and elements of DNA repair,[1] a recent article published in Cell Cycle by Huna and colleagues[2] establishes OCT4A as a multifunctional protein with a novel role as a major p53-dependent regulator of the DNA damage response (DDR) pathway. The latter activities occur in the absence of SOX2/NANOG response, i.e., independently of OCT4A's role in the stemness network. The report[2] sheds considerable light on the innermost workings of the DDR and its integration, a subject that has long been of great curiosity and ambiguity.[3] The findings (**Fig. 1**) provide insight into the nature of the pre-senescent transition state from which cells undergoing DDR ultimately execute cell-fate decisions – in this case, mitotic recovery versus "death" by terminal senescence or apoptosis. By silencing OCT4A and $p21^{Cip1}$ in PA-1 ovarian teratocarcinoma cells (which have a functional p53 axis) followed by exposure to etoposide, OCT4A was shown to suppress the levels and activity of $p21^{Cip1}$, whereas the reciprocal effect was not observed.[2] Like OCT4A, $p21^{Cip1}$ is a multi-functional protein; it is involved in activating cell cycle checkpoints, DNA repair, activating the "accelerated" senescence response to DNA damage, blocking apoptosis, and regulating the WIP1 phosphatase.[6] These observations indicate that OCT4A is an important regulator in the p53/DDR pathway that especially controls the $p21^{Cip1}$ protein and its various effects on the cell; however, it clearly exerts additional $p21^{Cip1}$-independent activities, such as in establishing the G2/M-arrested pre-senescent transition state itself.

The results further suggest that OCT4A functions in tandem with AMPK in directing cell-fate decisions in this cancer model, notably the evolution of the senescence phenotype; this complex process in part involves the AMPK/autophagy-driven cytoplasmic sequestration of $p16^{Ink4a}$, which is a mediator of the transition from pre- to terminal senescence, redirecting some cells toward mitotic recovery. These events represent a compelling target for therapeutic intervention by overcoming the resistance of cancer stem cells to DNA-damaging anticancer agents. Indeed, Huna et al.[2] note that in some scenarios the application of drugs that modulate AMPK/autophagy might serve to redirect chemotherapy-refractory tumor cells into an apoptotic death pathway. This strategy is

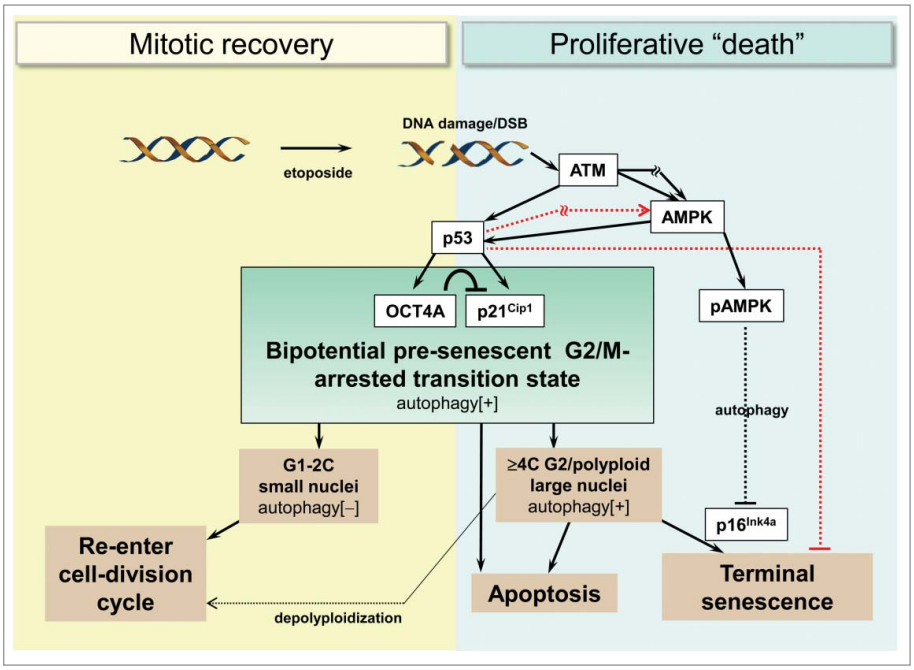

Figure 1. Cell-autonomous events in PA-1 cells treated with etoposide, based on Huna et al.[2] The G2/M-arrested transition state (OCT4A[+]/$p21^{Cip1}$[+]) has characteristics of both self renewal and senescence. OCT4A suppresses $p21^{Cip1}$ and senescence while enhancing mitotic recovery. Note the reported roles of p53 in both promoting and blocking senescence[4] and of AMPK in activating the p53 axis in response to DNA damage.[5]

certainly worth testing. The findings also inform treatment strategies that target the therapy-induced senescence phenotype in cancer cells which has a complex, often negative, relationship to therapeutic outcome.[7] Molecular insight such as that provided by Huna et al[2] might ultimately allow such decisions to be made on a rational mechanistic basis.

As Huna and colleagues[2] emphasize, these OCT4A-mediated contributions to the DDR have to date only been characterized for a single cancer cell line, PA-1, and a single anticancer drug, etoposide. It will thus be vital to establish the generality or exclusivity of these roles in cell lines derived from other tumor sites (including those with differing p53/$p16^{Ink4a}$ status) as well as in response to other classes of DNA-damaging agents, and indeed to other stress stimuli. It should also be noted that the current study focuses on a high dose of etoposide resulting in a population of cells with extensively damaged genomes of which few (~1%) are destined to emerge from the hypothetical metastable "bipotential" presenescent state, undergo mitotic recovery and "survive;" what will happen over a range of lower doses will be of great interest in the clinical context.

An intriguing observation from this study[2] is the considerable molecular heterogeneity of the early damage-signaling response among individual cells that is suggested to underlie the bifurcation of cell fate decisions. Such heterogeneity reaffirms the criticality of undertaking such molecular time-course studies at the single-cell level, as was indeed done by Huna et al.[2]

The outstanding contribution of this research team that demonstrates a pivotal role for OCT4A and autophagy in cell-autonomous DDR-related cell fate decisions will hopefully encourage meaningful discussion and further unraveling of the complex signaling dynamics and relationships between self renewal, senescence and cell cycle checkpoints/DDR in cancer cells. Such insight into the responses triggered by therapeutic agents in different cancer cell types will be crucial for designing effective approaches for preventing and treating this devastating disease.

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