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Previews

Fanconi Anemia Genes, of Menders and Sweepers

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Reporting recently in *Cell*, Sumpter et al. (2016) provide evidence that Fanconi anemia (FA) pathway genes, which are mutated in the homonymous disease and are tumor suppressors known as damaged nuclear DNA "menders," also act as intracellular sweepers in selective virophagy and mitophagy.

Fanconi anemia (FA) is a very rare and complex genetic disease characterized by diverse congenital defects (i.e., short stature, developmental disabilities and several tissue abnormalities) and, in the majority of the cases, the development of cancer (mostly leukemia) or bone marrow failure. FA is the result of mutations in a group of proteins, among which the breast-cancer crucial genes BRCA1 and BRCA2, all involved in nuclear damaged-DNA repair. Due to these genetic alterations, the DNA repair machinery in FA patients is much less effective in response to stress, with the bone marrow being particularly sensitive to this defect. A consequence of this is chromosomic instability, manifestation of which is a high incidence of cancer. Recently in *Cell*, Sumpter and colleagues (2016) elegantly uncover a link between FA pathway genes and specific selective autophagy processes: cytosolic mechanisms for viral pathogens (virophagy) or mitochondria (mitophagy) degradation.

Autophagy is a *pan*cellular mechanism responsible for controlling cell quality in physiological conditions through the recognition and degradation of cellular components by double-membrane-engulfing structures (autophagosomes) that normally fuse with the lysosomal degradative machinery (Mizushima and Komatsu, 2011). Further, autophagy can be actively triggered or increased under specific cellular stress conditions, such as nutrient deprivation or organelle damage. It is thus considered an important cytoprotective and safeguard system for the cell. Alterations of this complex and highly regulated machinery often have serious pathological consequences for the organism, such as increased cancer development (Levine and Kroemer, 2008). Autophagosome targets can also be selectively chosen by the cell in response to specific cell needs (Rogov et al., 2014). For example, mitophagy removes damaged mitochondria and thus controls mitochondria quality (Abeliovich and Dengjel, 2016), whereas so-called virophagy is crucial for the cell defense from infections, by specifically targeting and digesting encapsulated viruses (Sumpter and Levine, 2011). Cargo selectivity usually comes from specific autophagy receptors (e.g., p62 or Optineurin, with others probably still unidentified), which recognize cargoes tagged with degradation signals (Rogov et al., 2014) and promote their clearance through the binding with LC3.

Defects in both selective autophagy genes and FA pathway genes share surprisingly similar profound and serious effects on the organism, including increased tumorigenesis. A group led by Beth Levine initially found some FA genes in a siRNA genome-wide screen for selective-autophagy regulators (Orvedahl et al., 2011). They analyzed this finding in depth, and Sumpter et al. (2016) now report new function for FA genes. Indeed, besides their role on DNA damage repair, Sumpter et al. provide evidence that FA genes also function specifically on selective autophagy, such as virophagy and mitophagy (Figure 1). Importantly, this function is genetically independent of FA roles on DNA repair, as proven by the use of a natural mutant (FANCC c.67delG), which is competent for mitophagy but not for nuclear DNA damage repair. Of note, Sumpter et al. (2016) focused their studies on the FANCC protein, although they do demonstrate that their findings could be extended to essentially all FA genes.

In their study, Sumpter et al. (2016) show in vitro and in vivo that FA genes are somehow required for targeting genetically distinct viruses (both ssRNA- and dsDNA-encoded) to autophagic structures by interacting with viral capsid proteins and most likely acting as specific cargoing components of the selective machinery. Indeeed, FA proteins must work differently from other known autophagic adaptors, because they do not interact with any of the Atg proteins (such as LC3) classically involved in this selective target recruitment. It is conceivable that the authors may have even identified an alternative Atg-independent pathway for driving cargoes to the autophagosomes. This aspect certainly needs further investigation to determine the exact mechanism involved. However, the identification of a new role for FA genes in the safeguard pro-survival process of selective autophagy remains of extraordinary relevance.

Besides virophagy, Sumpter and colleagues (2016) also show that multiple FA genes are required for mitophagic removal of damaged mitochondria in the context of mitochondrial quality control. Again, this process takes place with these molecules acting as noncanonical cargo adaptor proteins, despite their capability to interact with the crucial mitophagy E3 ubiquitin ligase Parkin. Of note, Parkin seems to be pivotal in concentrating FANCC to mitochondria upon mitophagy induction, whereas FANCC is not required for Parkin recruitment. It will be of strong interest for the field to better understand this FA-Parkin axis, in a context in which specific Parkin roles in mitophagy have

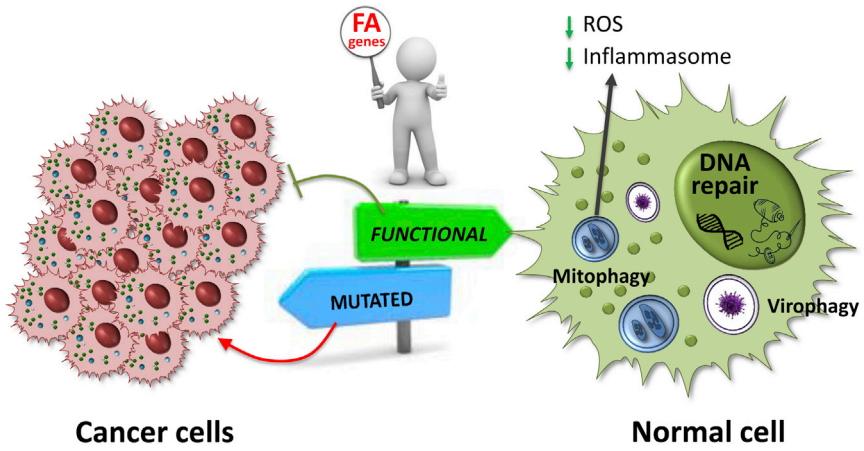

Figure 1. Fanconi Anemia Genes Also Function in Selective Autophagy
FA genes do not only act as cellular menders, as part of the DNA damage repair machinery, but also function in virophagy, to decrease viral infection, and in mitophagy, to decrease mitochondrial ROS production by damaged mitochondria (selective autophagosomes: mitophagy, blue; virophagy, purple). These functions impact on inflammasome activation. All of the independent FA functions act together to prevent bone marrow failure and cancer onset typical of Fanconi anemia disease. Mutation or absence of these FA gene functions increases the disease severity and promotes tumorigenesis.

been recently profoundly revised (Lazarou et al., 2015). Interestingly, by directly removing damaged mitochondria through mitophagy, FA genes inhibit the reactive oxygen species (mtROS) increase induced by damaged mitochondria, thus suppressing mtROS-triggered excessive activation of innate immune system receptors, globally known as the inflammasome response.

In our view, the major implication of this concerted "double-duty role" (to quote Sumpter et al.) for FA genes is the need to take into account potential effects on mitophagy (and potentially other forms of selective autophagy) in considering how mutations in FA genes contribute to the congenital syndrome regarding familial and sporadic cancers that they are associated with. As a first example, patients with the FANCC c67.delG mutation (which is still competent for mitophagy) exhibit a milder phenotype of FA syndrome and associated cancers. In contrast, both limb bud growth control and neuroepithelial proliferation during development could be affected by FA gene defects in either DNA repair or mitophagy, together or independently. Knowing this could better explain some complex patient phenotypes, such as thumb or limb anomalies and mental retardation, in those tissues where FA genes are expressed. Given the appreciated tumorigenic effect of disregulated mtROS production in different cancer types (Costa et al., 2014), FA gene function in mitophagy, inflammasome activation, and DNA damage repair could protect the organism against cancer, as well as against bone marrow failure. Conversely, defective FA genes that result in the inability to remove damaged mitochondria may lead to bone marrow failure and increased risk of malignancy in FA patients due to aberrant inflammasome activity, cell death, and accumulation of protumorigenic mutations (Figure 1).

Of the higest importance is exploring this DNA repair-independent function of FA genes, as it may provide a potential new avenue of inflammasome-targeting therapy for patients with diseases related to FA mutations. From a more clinical point of view, new FA agents targeting the inflammasome and the production of the pro-inflammatory cytokine interleukin 1 beta (IL-1β) could be extremely promising. Indeed, IL-1β signaling has already been very efficiently targeted in several auto-inflammatory diseases, such as rheumatoid arthritis, involving excessive inflammasome activation. The findings of Sumpter et al. (2016) suggest that FA patients may also benefit from these types of therapies.

Future work examining the potential overlap between the DNA repair and the autophagy functions of FA genes and their co-regulation and coordination will also be key. The DNA repair machinery may indeed crosstalk with autophagy in the global context of a cellular stress response. These findings regarding FA genes may represent a paradigm example of this *Janus*-faced mode of cellular control.

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