SLX4 gains weight with SUMO in genome maintenance

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ABSTRACT:
Replication stress has emerged as a key driver of oncogenesis but also represents an Achilles' heel of cancer cells. Newly reported SUMO binding and SUMO ligase functions of the DNA repair SLX4 protein that impact the outcome of replication stress open new avenues for investigating roles played by SLX4 in tumorigenesis.

Maintenance of genome stability is a humungous task for the cell that faces constant endogenous and exogenous genotoxic threats. For this it relies on elaborate DNA repair machineries that need to be coordinated with genome surveillance and cell cycle control mechanisms. Accumulating evidence indicates that many repair factors are not specific to a given DNA repair pathway leading to an emerging and key question: How does the cell channel in a timely manner these repair factors to the appropriate repair pathway and what may be the consequences for the cell should such control mechanisms be altered. Promising clues came a few years back with the identification of the human SLX4 protein (for review[1]); a scaffold that interacts with the XPF-ERCC1, MUS81-EME1 and SLX1 structure-specific endonucleases, the mismatch repair MSH2-MSH3 complex, the telomere maintenance protein TRF2 as well as with the cell-cycle control PLK1 kinase. This puts SLX4 at the cross-roads of several genome maintenance mechanisms with recently confirmed key functions in DNA interstrand crosslink (ICL) repair, the resolution of Holliday junctions during homologous recombination and the regulation of telomere homeostasis[1]. An unexpected role of SLX4 in the control of HIV infection and the innate immune response has also been reported[2]. These pivotal functions in genome maintenance are underscored by the fact that bi-allelic mutations in *SLX4* cause Fanconi Anemia[1], a syndrome associating bone marrow failure with cancer predisposition, revealing its fundamental role as a tumour suppressor, also supported by the cancer prone phenotype of mice models[3].

New insight into how SLX4 might control and channel the action of its partners into various DNA repair pathways has now been provided with the realization that it has SUMO binding properties [4,5] and is an essential component of a SUMO E3 ligase that SUMOylates SLX4 itself as well as the XPF subunit of the XPF-ERCC1 structure-specific nuclease[5].

These SUMO-related functions of SLX4 are mediated by a newly identified cluster of SUMO-Interacting Motifs (SIMs) that provide SLX4 with the ability to efficiently bind poly-SUMO chains in vitro and SUMOylated proteins in vivo[4,5]. Unexpectedly, they also turn out to mediate a remarkably specific interaction between SLX4 and the active SUMO-charged form of the SUMO E2 conjugating enzyme UBC9 but not its unmodified or

SUMOylated forms[5]. This specific interaction, which involves hydrophobic SIM-SUMO interactions as well as electrostatic interactions between negative charges within SLX4 SIMs and the basic patch of UBC9, is essential for the SUMO E3 ligase activity of the SLX4 complex. This, along with the fact that SUMO ligase activity of the SLX4 complex also relies on the BTB domain of SLX4, strongly suggests that SLX4 itself acts as a SUMO E3 ligase. Confirmation for this awaits that SLX4-mediated SUMO ligase activity can be reconstituted in vitro with fully recombinant proteins. Not a trivial task, considering that full SUMO ligase activity, which for now has been successfully monitored in vitro with SLX4 complexes immunoprecipitated from human cells, relies on both salt-labile co-factors and protein phosphorylation[5].

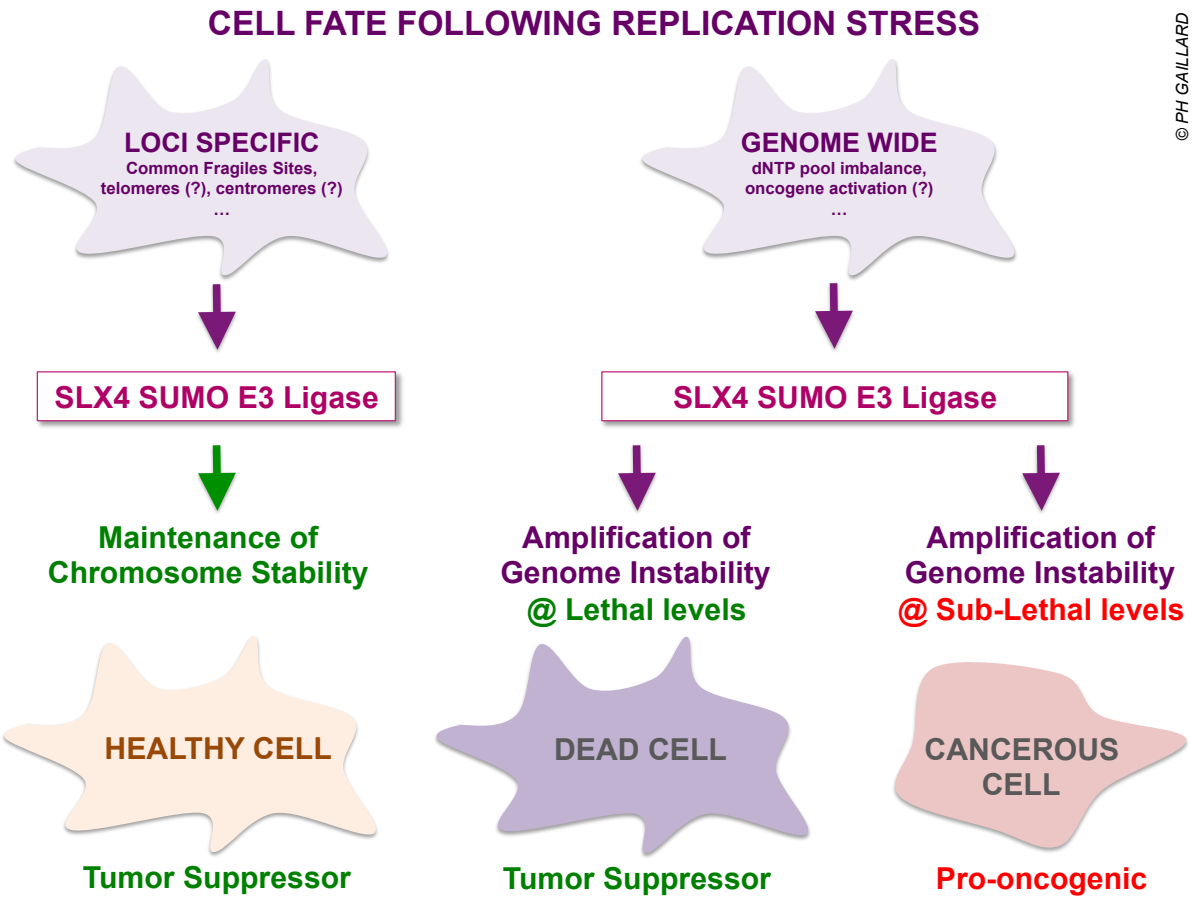
Interestingly, while SLX4 also has ubiquitin binding properties that are essential for ICL repair[1], its SUMO-related functions are not[4,5]. Instead they channel the SLX4 complex down another route that deals with the maintenance of common fragile site and probably other loci that are prone to replication stress such as telomeres and centromeres[4,5]. Amazingly, when replication stress is pan genomic following treatments with hydroxyurea, alone or combined with ATR inhibition, the SUMO-related functions of SLX4 turn out to promote genome instability and cell death and are responsible for the double strand breaks previously reported to be induced by SLX4 in response to replication stress [5-7].

Counter-intuitively though, the cytotoxic effects of the SUMO-related functions SLX4 relies only partially on its nuclease partners. Nuclease-independent functions have been ascribed to budding yeast Slx4 which plays an anti-checkpoint role through its interaction with Rtt107 and Dpb11^{TOPBP1} [8]. Interestingly, the PLK1 kinase (another direct partner of SLX4) also promotes replication fork collapse and DSBs in ATR-deficient cells upon replication stress[7].

Since oncogene activation triggers chronic replication stress, the cytotoxic role played by SLX4 in response to genome wide replication stress might be part of its tumor-suppressor functions (Figure 1). A similar role in the clearance of cells that have sustained severe replication stress has recently been suggested for the FBH1 helicase[9,10]. Loss of SUMO-dependent functions of SLX4 may thus result in the loss of an important tumor-suppressing barrier and allow the escape of oncogene-induced senescence. However, amplifying genomic instability in the face of acute or chronic replication stress is a dangerous strategy where the line between tumor-suppressor and pro-oncogenic outcomes is scaringly thin. Just like using controlled burns to circumvent wildfires, it has to be applied in a controlled manner and taken all the way to cell death or it might instead add insult to injury and fuel the emergence of cancerous cells (Figure 1). Adding to the dangerosity of the picture, SLX4 has recently been shown to suppress innate immunity[2], another important early barrier to tumorigenesis. While the identification and characterization of the SUMO binding and SUMO ligase properties of SLX4 adds new pieces to the puzzle, the complexity of the emerging picture comes with new and fascinating questions that are already begging for answers.

FIGURE LEGEND:

Figure 1: The SUMO E3 ligase activity of the SLX4 complex differentially impacts cell fate after loci specific or genome wide replication stress.
The model includes speculations discussed in the text on how the newly described SUMO-related functions of SLX4 walk on a thin line between tumor-suppressor and pro-oncogenic outcomes.



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