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Cell-to-cell transmission of p53 aggregates: a novel player in oncology?

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ABSTRACT

The mutants of the tumor suppressor protein p53 form protein aggregates. It has been proposed that these aggregates propagate like prions, albeit the detailed mechanism of the propagation is unclear. Our recent study revealed that sulfated glycosaminoglycans, especially highly sulfated domains of heparan sulfate (heparan sulfate S-domains), participate in cancer pathology by mediating transcellular propagation of p53 aggregates.

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Tumor protein p53 (TP53, best known as p53) is a product of the *TP53* gene, which is mutated in >50% of all human cancer cases. It has been shown that p53 form amyloid-like aggregates in human cancer tissues and *in vitro*,¹ suggesting that p53-mutant cancers represent a new class of protein aggregation diseases, as also mentioned in the Amyloid Nomenclature 2020.² Although p53 aggregates have been proposed to exhibit prion-like cell-to-cell transmission, similar to that of several other protein aggregates,² which molecules are actually involved in the cell-to-cell transmission remains to be elucidated. Sulfated glycosaminoglycans (GAGs) have been implicated in the pathology of diseases that are associated with protein aggregates by promoting the formation and cellular interaction of protein aggregates.³ GAGs are linear and unbranched polysaccharides that form proteoglycans by attaching to the core protein. The GAG family includes heparan sulfate (HS), chondroitin sulfate (CS), and keratan sulfate. Certain domains within the HS chains are highly sulfated (HS S-domains) and involved in several biological and pathological processes, including these cancers. These HS S-domains deposit together with amyloid deposits, such as those of A β in Alzheimer's disease and transthyretin (TTR) in familial transthyretin amyloidosis (ATTR amyloidosis).^{4,5} Moreover, it has been proposed that the patterns and degrees of GAG sulfation are essential for the pathology and progression of systemic and localized amyloidoses.⁶ Indeed, we previously revealed that HS S-domains co-deposit together with amyloid fibrils and are an essential mediator of the pathologies of Alzheimer's disease, apolipoprotein A-I amyloidosis, and ATTR amyloidosis.^{5,7} In a recent study by Iwahashi et al., we extended the role of HS S-domains as the mediator of cell-to-cell transmission of protein aggregates to include those of p53.⁸

Iwahashi et al. reported that HS S-domains represent a nonprotein component of p53 deposits in ovarian cancer tissues, which supports that certain types of cancers with p53

deposits are protein aggregation diseases. In this study, we took advantage of the techniques in glycobiology, that is, the variants of Chinese hamster ovary (CHO) cells that lack both HS and CS or only HS; β -xyloside that eliminates proteoglycan forms of GAG chains from the cell surface, sodium chlorate that inhibits the sulfation modification of GAGs, and heparin, which is a structural analogue of HS S-domains and competitively inhibits the cell uptake of various protein aggregates. We first found that amyloid fibrils of *Escherichia coli*-expressed wild-type, full-length, p53 protein were taken up in a sulfated GAG-dependent manner. We next examined the cancer cell-derived p53 aggregates. We found that the OVCAR-3 human ovarian carcinoma cells carry the p53 R248Q mutation and form p53 aggregates within cells, and, as expected, OVCAR-3 cells extracellularly released mutant p53 amyloid fibrils. Again, the cellular uptake of OVCAR-3 cell-released p53 aggregates depended on the sulfated GAGs and HS on the cell surface. As an interesting characteristic, HS S-domains could be post-synthetically remodeled by human SULFs, endoglucosamine 6-sulfatases, by removing the 6-O-sulfates. In the CHO cells whose HS S-domains were eliminated by the stable expression of human SULF2,^{5,7} the cell uptake of both recombinant p53 fibrils and cancer cell-derived p53 aggregates depended on the HS S-domains at the cell surface, which strongly supports the role of sulfated GAGs, especially HS S-domains, as a universal receptor of various protein aggregates.⁶ A past report demonstrated that sulfated GAG-dependent extracellular release of pathological Tau via the unconventional secretion encouraged us to investigate the role of sulfated GAGs in the extracellular release of p53.⁹ p53 protein secretion from OVCAR-3 cells and another p53-mutated MDA-MB-231 cells depended on sulfated GAGs at the cell surface, which extended the function of sulfated GAGs to include the extracellular p53 export.

The final question was regarding the involvement of cell-to-cell transmission of p53 aggregates in the cancer pathology.

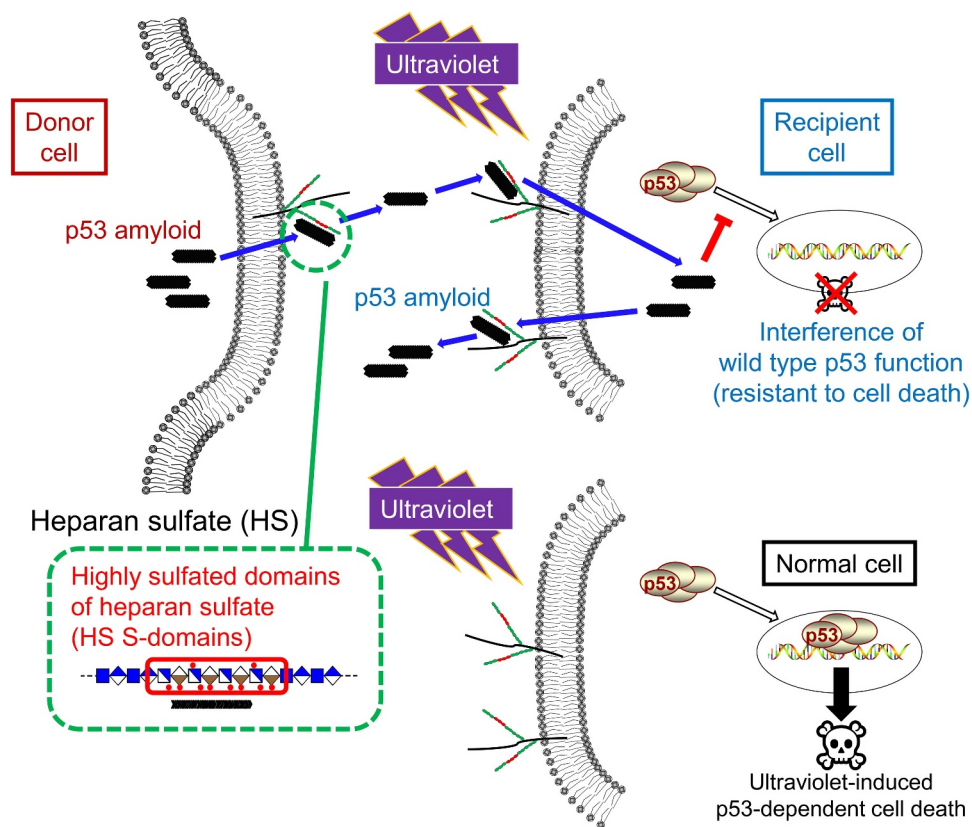


Figure 1. Potential role of sulfated GAGs and HS S-domains in cell-to-cell transmission of p53 aggregates. Donor cells release p53 aggregates in a sulfated GAG-dependent manner, and the recipient cells take up the p53 aggregates. In this uptake process, the HS S-domains act as a receptor for p53 aggregates and thus play a critical role in cell-to-cell transmission of p53 aggregates. In cells with functional p53, irradiation with ultraviolet (UV) induced cell death, while the recipients of p53 aggregates did not die, presumably because the p53 aggregates interfered with the functions of wild-type p53.

Iwahashi et al. reported that sulfated GAG-mediated cell uptake of p53 aggregates is critical for cell-to-cell transmission. We further queried whether p53 aggregate-containing cells exhibit a gain-of-oncogenic function phenotype by using A549 p53 WT cells as a model for cells with normal p53 functions. A549 cells that took up cancer cell-derived p53 aggregates displayed reduced ultraviolet-induced cell death when compared to cells treated with the p53-free fraction of OVCAR3 CM, which was reversed by inhibiting the cellular uptake of p53 aggregates using heparin.

In summary, we proposed a line of functions of sulfated GAGs in cell-to-cell transmission of p53 aggregates, that is, sulfated GAGs, especially HS S-domains, was found to play a critical role by acting as a mediator of extracellular release and cell uptake (Figure 1). These findings expand the proposal of sulfated GAGs as a common mediator of protein aggregation propagation to p53 aggregation-associated cancers. Our findings also raise the notion that enzymatic remodeling of HS S-domains can represent a potential strategy for targeting the transcellular propagation of p53 aggregates, as already proposed for other amyloidoses.¹⁰

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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