CANCER

Mutant p53 rescued by aggregation inhibitor

> p53-mutant tumours exposed to ReACp53 were 80–90% smaller than corresponding tumours in control-treated animals

TP53, the gene encoding the tumour suppressor p53, is lost or mutated in approximately one-half of all human cancers, and over 96% of high-grade serous ovarian carcinomas (HGSOCs) express mutant p53. Some of these mutations lead to aggregation of p53 into an amyloid-like state, abrogating its transcriptional activity and pro-apoptotic functions. Now, reporting in *Cancer Cell*, Soragni and colleagues present a peptide inhibitor of p53 aggregation that can rescue p53 function and shrink tumours in mouse models of HGSOC.

Some frequently observed mutations in p53 appear to destabilize the native protein structure and expose a 'sticky' sequence that can bind to identical segments in other destabilized p53 proteins, leading to protein aggregation. The authors hypothesized that by masking this sequence, aggregation may be prevented. Computational algorithms to identify the most aggregation-prone segments of p53, followed by a structural analysis of the aggregated state of these peptides, then informed the design of aggregation inhibitors.

In vitro experiments using primary human HSGOC cells with various *TP53* mutations showed that such 'masking peptides', fused to a cell-penetrating polyarginine tag, can readily affect the localization and function of mutant p53. For example, HSGOC cells carrying the p53 R248Q mutation contained very little p53 in the nucleus and had aggregates of p53 in the cytosol. After 16–20 hours of incubation with the peptide ReACp53, these aggregates largely disappeared, and p53 was mainly detected in the nucleus. ReACp53 also reduced the viability of these cells in a concentration-dependent manner, whereas a sequence-scrambled control peptide or the polyarginine tag alone was ineffective. ReACp53 also appeared to re-establish the interaction of p53 with MDM2 — a ubiquitin ligase that negatively regulates p53 levels — and a combination of the MDM2 inhibitor nutlin and ReACp53 showed synergistic cell killing.

Using a more physiological 3D culture system, the authors also demonstrated that ReACp53 can re-activate normal p53 transcriptional activity in p53 mutant cells. Interestingly, several metabolic pathways were downregulated in response to ReACp53 treatment — including the mevalonate pathway, which is known to promote cell migration and invasion in ovarian cancer.

Next, ReACp53 was tested in mice implanted with matrigel-embedded *TP53*-wild-type HGSOC cells in one flank and *TP53*-mutated HGSOC cells in the other. Animals received daily intraperitoneal (i.p.) injections of ReACp53 for 3 weeks — either starting on the day of tumour cell injection or after allowing the tumours to grow for 2 weeks. In both cases, p53-mutant tumours exposed to ReACp53 were 80–90% smaller than corresponding tumours in control-treated animals. By contrast, the growth of the p53-wild-type tumours was not affected. Importantly, the treatment was well tolerated.

ReACp53 was also investigated in a mouse model of disseminated disease, induced by i.p. injection of *TP53*-mutated HGSOC cells. The animals develop ascites and tumour growth in various organs within 2 weeks. After four daily injections of ReACp53, 80% of tumour cells in the peritoneal cavity were apoptotic. After 3 weeks of daily treatment, very few tumour cells remained in the peritoneal cavity and tumour-spread to organs was significantly reduced.

These experiments suggest that cancers with aggregation-prone p53 mutants could be treated as protein-aggregation diseases. As the p53 pathway can be activated by DNA damage, the authors suggest that such an approach might be particularly effective when combined with DNA-damaging agents.

Alexandra Flemming

Paul Fleet/Alamy Stock Photo

ORIGINAL ARTICLE Soragni, A. *et al.* A designed inhibitor of p53 aggregation rescues p53 tumour suppression in ovarian carcinomas. *Cancer Cell* **29**, 90–103 (2016)