outline

RESTORING PROTECTION

Many tumours exhibit dysfunction of the p53 protein, a crucial suppressor of cancer. But, because the cause of this dysfunction varies, so, too, must potential treatments.

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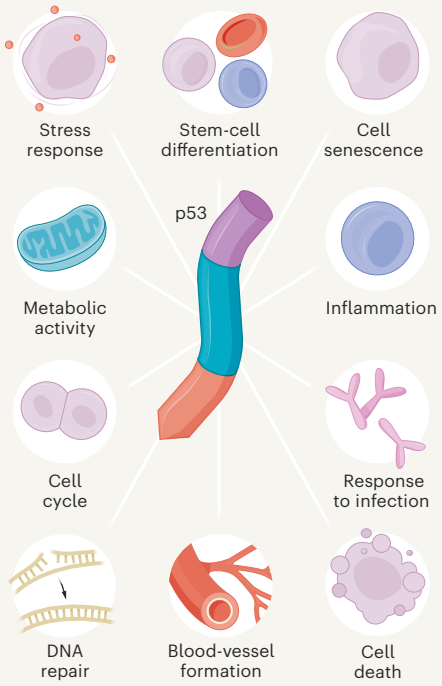
p53 THE VIP

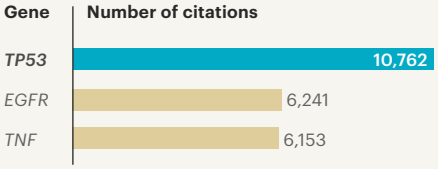
The p53 protein is involved in a dizzying array of healthy physiological functions. In many cases, p53 controls these functions by regulating gene expression.

p53 directly regulates more than **300 GENES** with many more indirectly affected[1].



CENTRE OF ATTENTION

The gene that produces p53 (known as *TP53*) is the most well-studied gene in the human genome, having been cited in more than 10,000 papers since its discovery in 1979 (ref. 2).

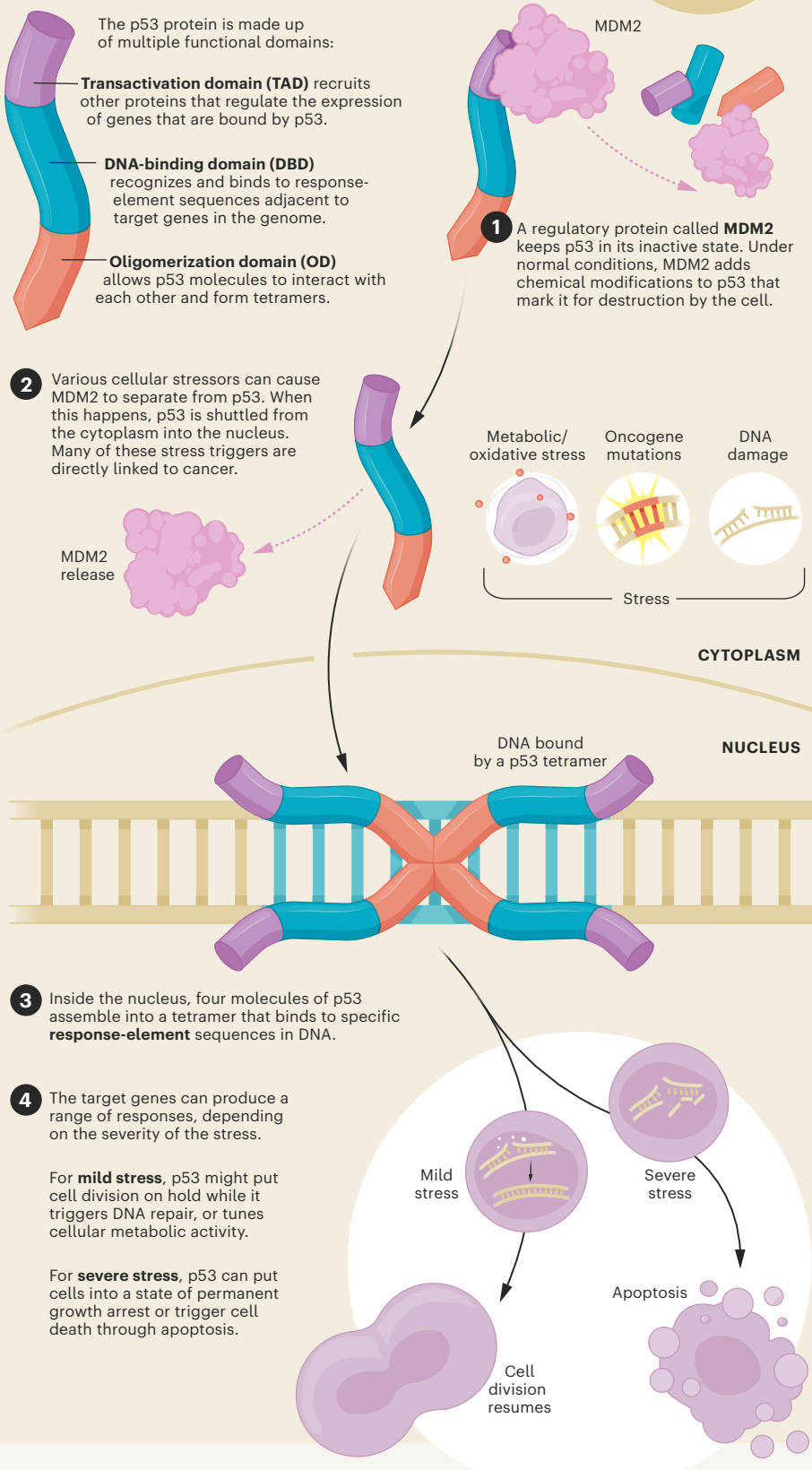


Data from NCBI-NLM as of 25 January 2022.

A HEALTHY FUNCTION

Healthy cells express low levels of p53. The protein is normally trapped in an inhibited state, and these inactive p53 molecules are swiftly broken down.

Inactive p53 molecules have an average half-life of just **9 MINUTES**[3].



Watch an animation at go.nature.com/collections/p53-outline

BROKEN OR BLOCKED

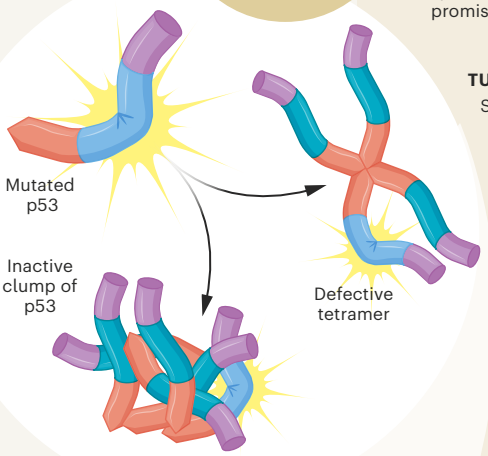
The function of p53 can be lost owing to mutations in the *TP53* gene, or because of the dysfunction of proteins that regulate p53. In either case, these problems give cancer the green light to progress.

The *TP53* gene is mutated in more than **50%** of tumours[4].

TUMOURS WITH MUTANT p53

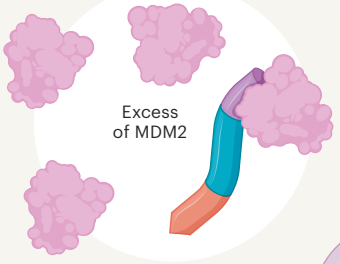
Around 80% of p53 mutations affect amino acids in the protein's DBD, causing it to misfold and also interfering with the recognition of target genes[4].

Even one mutated copy of *TP53* can fuel tumour formation, given that a defective p53 protein combined with other, normal p53 proteins will form a non-functional tetramer. Some studies suggest that mutant p53 also inflicts damage by accumulating as aggregates of misfolded proteins[5].



TUMOURS WITH WILD-TYPE p53

Even if *TP53* is not mutated, p53 function can still be disrupted. For example, some tumours produce excessive MDM2 that keeps p53 trapped in an inactive state.

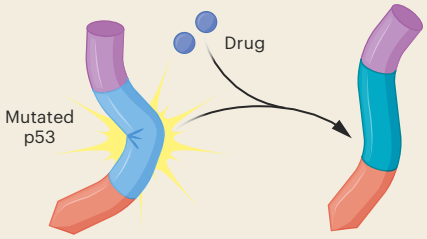


A CHANCE OF TREATMENT

Even after 40 years of research, clinicians still lack drugs that can specifically target tumours with p53 dysfunction. But several promising therapeutic strategies are now undergoing trials.

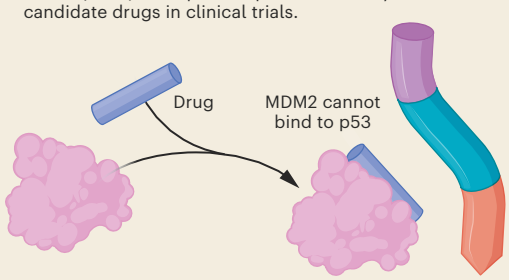
TUMOURS WITH MUTANT p53

Some small-molecule drugs can bind mutant p53 in a way that restores normal folding. Several such drugs are now in preclinical or early-stage clinical development[6]. However, this approach requires therapy to be tailored to each patient's particular *TP53* mutation.



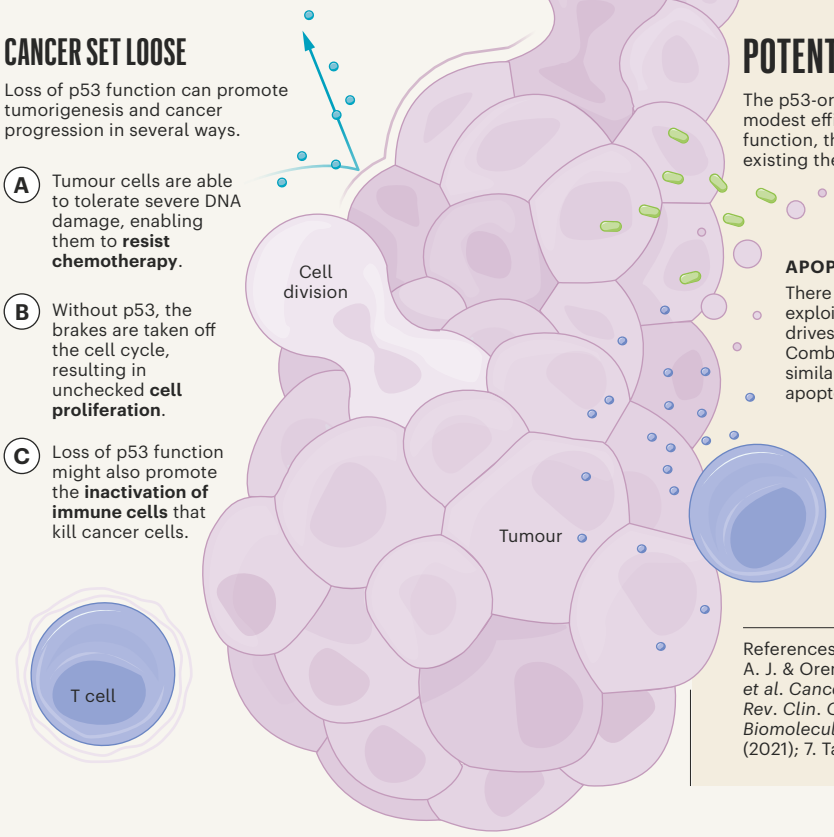
TUMOURS WITH WILD-TYPE p53

Drugs that block MDM2's ability to inhibit p53 might offer a solution for tumours that produce an excess of MDM2 (ref. 7). Multiple companies currently have such candidate drugs in clinical trials.



CANCER SET LOOSE

Loss of p53 function can promote tumorigenesis and cancer progression in several ways.



POTENT PARTNERS

The p53-oriented drugs tested so far have shown minimal or modest efficacy on their own. But by helping to normalize p53 function, these drugs could be used in combination with existing therapeutic strategies to give them a boost.

APOPTOSIS INDUCERS

There are multiple proteins that tumour cells can exploit to inhibit cell death. Restoring p53 function drives the degradation of one of these, known as MCL-1. Combining this treatment with drugs that knock out similar proteins, such as BCL-2, might therefore promote apoptosis more effectively than either treatment alone.

IMMUNE-CELL ACTIVATORS

The loss of p53 function puts tumours into an immunosuppressed state. Restoring normal function could prime tumours to respond to drugs such as the checkpoint inhibitor pembrolizumab.

References: 1. Fischer, M. *Oncogene* **36**, 3943–3956 (2017); 2. Levine, A. J. & Oren, M. *Nature Rev. Cancer* **9**, 749–758 (2009); 3. Gomes, A. S. *et al. Cancers* **13**, 3344 (2021); 4. Sabapathy, K. & Lane, D. P. *Nature Rev. Clin. Oncol.* **15**, 13–30 (2018); 5. de Oliveira, G. A. P. *et al. Biomolecules* **10**, 548 (2020); 6. Hu, J. *et al. J. Hematol. Oncol.* **14**, 157 (2021); 7. Takahashi, S. *et al. Cancer Sci.* **112**, 2361–2370 (2021).