The consequences of improper DNA-maintenance overlap – at least partially – with those of a disrupted protein homeostasis. Indeed, both are associated with neurodegeneration, and both are thought to play an important role in ageing. In our research we therefore investigated whether improper DNA-maintenance challenges protein homeostasis.

We found that distinct defects in DNA-maintenance indeed lead to a disrupted protein homeostasis and widespread protein aggregation. Proteins that aggregate are not random proteins, but are intrinsically vulnerable. Normally, such proteins are protected against aggregation by a group of highly specialized guardian proteins, called chaperones.

In cells and worms in which we artificially enhanced chaperone capacity, protein aggregation was no longer increased upon improper DNA-maintenance. Moreover, worms with an enhanced chaperone capacity no longer suffered from accelerated age-related degeneration induced by improper DNA-maintenance.

These findings show that upon impaired DNA-maintenance the chaperone capacity in cells is overwhelmed. How this happens exactly is still unclear. Eventually, this leads to a disrupted protein homeostasis and widespread protein aggregation. This process appears to play a key role in the acceleration of age-related degeneration ensuing improper DNA-maintenance.

The findings of our study point at a crucial two-stage mechanism: various impairments in DNA-maintenance result in a disrupted protein homeostasis, and this in turn accelerates age-related degeneration. Our data also indicate that DNA-damage itself can trigger this process.

Although more research is needed, this knowledge promises to contribute greatly to our understanding of DNA-repair syndromes. It is also highly relevant for the general population. It puts the spotlight on a long underexposed, but potentially very important role of DNA-damage and compromised DNA-repair, both in common neurodegenerative diseases and in normal ageing.