Parkinson’s disease (PD) is a common disease which affects the nervous system, causing bradykinesia (slowness of movement), rigidity (muscle stiffness), tremor (twitching) and postural instability. The symptoms of PD are caused by the progressive death of cells in the brain that create dopamine, which acts as a messenger that tells a different area of the brain to move a part of the body. People with PD also have abnormal clumps of protein in the brain called Lewy bodies, although it is unclear what role these play.

Although PD often occurs randomly (sporadic PD), it is hereditary in some families. Mutations of a chemical called alpha-synuclein have been found in different families with PD. These mutations can cause an autosomal dominant form of PD, meaning that if one of your parents has the mutated form, you will develop PD. Alpha-synuclein is also found in the Lewy bodies of people with sporadic PD, suggesting that it has an important role in the disease’s development.

We have demonstrated that alpha-synuclein interacts with a protein we have named synphilin‑1. This interaction leads to the formation of clumps of proteins that resemble Lewy bodies. We also found that synphilin-1 is degraded by an enzyme called E3 ubiquitin-protein ligase SIAH1, through the ubiquitin-proteasome system. Ubiquitin is a small protein whose bonding with other proteins (in this case synphilin-1), known as ubiquitination, targets them for degradation by proteasomes; if the proteasome is unable to degrade the ubiquitinated synphilin-1, clumps containing both synphilin-1 and SIAH form inside the brain cells and attract alpha-synuclein.

We discovered that SIAH produced naturally by the body ubiquitinates alpha-synuclein, and that the parts of the molecule ubiquitinated by SIAH are the same as those ubiquitinated in alpha-synuclein purified from Lewy bodies. We also found that degradation of alpha-synuclein through the ubiquitin-proteasome system is influenced by USP9X, an enzyme which cleaves the bond between ubiquitin and alpha-synuclein. When alpha-synuclein is ubiquitinated, it is degraded by proteasomes; in contrast, when its ubiquitin has been cleaved by USP9X, it is degraded through natural processes. This suggests that the fate of alpha-synuclein depends on the level of USP9X.

More recently, we found that a chemical called PIAS2 “SUMOylates” (inhibits the degradation of) alpha-synuclein, leading to its increased accumulation and causing it to clump - a process known to be involved in PD, as noted above. The brains of PD patients contain higher levels of SUMOlyated alpha-synuclein and PIAS2, and the alpha-synuclein mutations found in their brains are in fact more readily SUMOlyated.

Our findings suggest that USP9X and PIAS2 could be new targets in preventing the accumulation of pathological alpha-synuclein in PD. We are also currently studying the structure of ubiquitinated and SUMOylated alpha-synuclein to enable a computerized search for compounds that can degrade alpha-synuclein more efficiently through the proteasome pathway.