Molecular mechanism of genetic compensation response

With the support by the National Natural Science Foundation of China, the research team led by Prof. Chen Jun (陈军) at the MOE Key Laboratory of Biosystems Homeostasis & Protection and Innovation Center for Cell Signaling Network, College of Life Sciences, Zhejiang University, uncovered the molecular mechanism of genetic compensation response (GCR), which was published in *Nature* (2019, 568(7751): 259—263).

GCR is considered a genetic paradox and was firstly described in zebrafish to explain a phenomenon of the phenotypic discrepancies between gene-knockout and -knockdown in 2015, whereby the knockout of a gene sometimes has no observable impact due to the transcriptional upregulation of related genes, whereas the knockdown of the same gene does not trigger the GCR, in turn to result in major defects. This phenomenon was also found in other model systems including mice and *Arabidopsis*. However, the underlying molecular mechanism of the GCR remains elusive.

Prof. Chen's team used two zebrafish mutants carrying a premature termination codon (PTC), *capn3a*$^{-/-}$ (a cysteine proteinase) and *nid1a*$^{-/-}$ (a basement membrane protein) as gene compensation models. Both of the mutants do not exhibit any obvious phenotypes due to upregulation of its family members in each mutant, which is different from those of embryos with the knockdown of either *capn3a* (displaying small liver) or *nid1a* (showing short body length). By analyzing six uniquely designed transgenes, they demonstrated that the GCR was dependent upon both the presence of a PTC and the nucleotide sequence of the transgene mRNA that is homologous to the compensatory endogenous genes. Since mutations producing a PTC are required to trigger a GCR, they speculated that the nonsense-mediated mRNA decay (NMD) pathway might be involved in GCRs. Through gene knockdown and knockout of the key factors of NMD pathway, they demonstrated that only *upf3a* (a weak mediator of NMD), but not *upf1* and *upf3b* (promoters of NMD), was required for the GCR. Furthermore, they revealed the GCR was accompanied by an enhancement of H3K4 trimethylation (H3K4me3) in the transcription start site (TSS) regions of the compensatory genes. They also identified that Wdr5, a component of COMPASS complex, interacted with Upf3a, and was required for the GCR by mediating H3K4me3 at the promoters of compensatory genes. These findings not only provide a potential mechanistic basis for the GCR (Figure), but also for overcoming the obstacle of GCRs in gene function studies and developing novel therapeutic strategies in treating missense mutations associated with genetic disorders through either creating a PTC in the mutated gene or by introducing a transgene harboring a PTC to trigger a GCR.

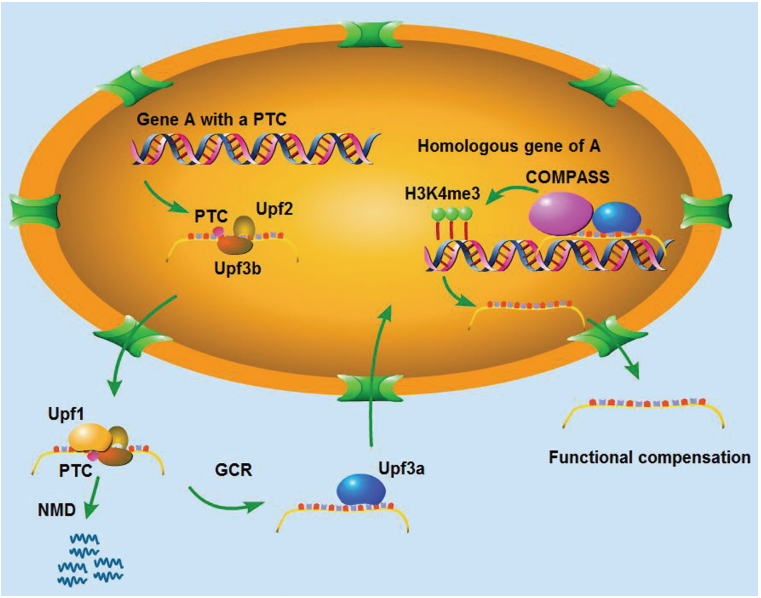

Figure A proposed model for genetic compensation response.