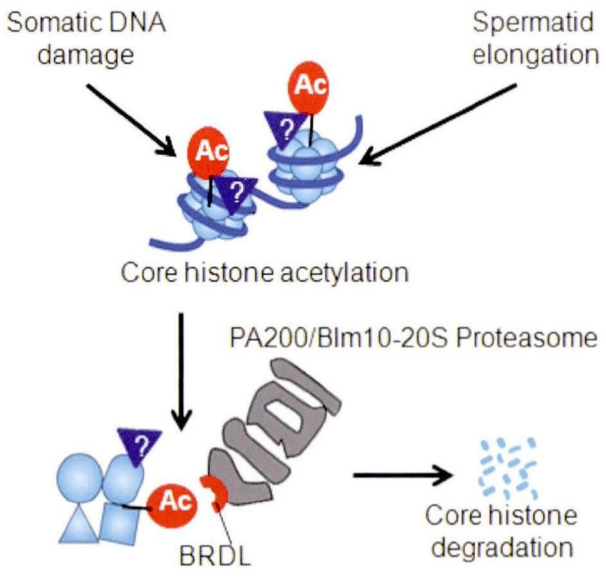
NSFC funded researchers achieved major breakthroughs in acetylation-mediated degradation of core histones



Acetylation-Mediated Degradation of Core Histones

Acetylation is a major type of protein post-translational modification, and is found in more than 7,000 human proteins (*FEBS Lett* **2012**, 586: 2692). It regulates many critical cellular activities, such as epigenetic regulation of gene expression, DNA repair, and spermatogenesis. However, the mechanism by which acetylation regulates these critical processes remains unclear. Proteasomes catalyze ATP- and polyubiquitin-dependent degradation of most cellular proteins (*Physiol Rev* **2002**, 82: 373; *Nature* **2003**, 426: 895). However, the ubiquitin enzymes, which catalyze the polyubiquitin-mediated degradation of histones, have not yet been identified (*Dev Dyn* **2007**, 236: 2889). Funded by NSFC and Ministry of Science & Technology of China, a group led by Dr. Qiu Xiaobo at Beijing Normal University demonstrated that the specialized proteasomes containing the activator PA200/Blm10 catalyze the acetylation, rather than ubiquitination, -mediated degradation of the core histones, revealing mechanisms for acetylation in histone degradation, spermatogenesis, and DNA repair. Their results have recently been published in *Cell* (**2013**, 53: 1012).

The core histones form an octamer to pack DNA into the nucleosome, which is the unit of chromatin organization. Histones are usually synthesized during DNA replication, are proposed as the carriers of epigenetic information, and were once believed to be non-degradable in somatic cells. Dr. Qiu's group demonstrated that the core histones are degradable in both somatic and spermatogenic cells, and are the first physiological substrates identified thus far for the PA200/Blm10-containing proteasomes. They showed that most proteasomes in mammalian testes (referred to as spermatoproteasomes) contain a spermatid/sperm-specific-subunit α4 s and/or the catalytic β-subunits of immunoproteasomes in addition to PA200, and that PA200/Blm10, by serving as a proteasome activator, is required for the timely removal of the core histones during somatic DNA damage and spermatogenesis. This novel type of the proteasome in the testis represents the first tissue-specific proteasome. Furthermore, they discovered atypical bromodomains in PA200/Blm10 that recognize the acetyllysine residue on the core histones. These findings could be important for the development of drugs against certain types of tumors or even male contraceptives. Numerous histone deacetylase inhibitors are under investigation in clinical trials as anticancer agents, especially in conjunction with other treatments such as chemotherapy and radiation therapy (*J Cell Mol Med* **2011**, 15: 2735). They showed that histone deacetylase inhibitors potentiate the acetylation-mediated histone degradation induced by radiation or the DNA-damaging agent, providing a mechanism that may contribute to the clinical applications of these inhibitors.