Modulating the Ubiquitin System with Cyclic Peptides: Chemistry and Biology

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The ubiquitin (Ub) signal plays crucial roles in various cellular activities such as cell cycle regulation, DNA damage repair, signal transduction, neural development and transcription. It is therefore not surprising that there is a great interest in targeting various components involved in the Ub pathway such as deubiquitinating enzymes (DUBs) and the 26S proteasome with the aim of producing novel drugs against several diseases. For nearly a decade my laboratory has been interested in developing chemical tools to assist in understanding Ub signaling in great details, allowing also for the development of novel modulators for its components. In particular, we have been interested in developing assays, activity-based probes and inhibitors for DUBs. In this talk, I will describe our efforts in applying the Random Non-Standard Peptides Integrated Discovery method (RaPID), developed by the Suga laboratory, to discover novel cyclic peptides that specifically bind Lys48-linked or Lys63 linked Ub chains. The discovered cyclic peptides were found to protected Lys48-linked Ub chains from DUBs activity and prevented proteasomal degradation of Ub-tagged proteins. We also found that these cyclic peptides could enter cells, inhibit growth and induce programmed cell death. Finally, these cyclic peptides were also active in an animal model, therefore opening new opportunities for therapeutic intervention. On the other hand, the cyclic peptides that modulate Lys63-linked Ub chains were found to interfere with the DNA repair mechanism. Finally, I will present our recent efforts for the development of new methods of peptide cyclization using Gold(I) chemistry.

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