Chemistry, Biology and Pharmacology of Novel Covalent Protein Modifications

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Abstract

Our understanding of how the biology of various diseases relates to the central dogma that DNA encodes RNA, which encodes protein has been buoyed by rapid technological advances in DNA and RNA sequencing and has led to some of the first advances in personalized medicine. However, characterization of the final and arguably most actionable element of the central dogma, protein, has lagged behind. Among the various proteomic parameters, a comprehensive description of the landscape of covalent protein modifications in any given cell is particularly challenging. Our research efforts are highly multidisciplinary, which have been largely focused on two programs, i.e., (1) novel protein posttranslational modifications (PTMs), and (2) novel covalent protein modifications by small molecule drugs. The entire repertoire of protein posttranslational modifications (PTMs) is enormous, with ~400 different known types, and many more unknown ones (i.e., the “dark proteome”). PTMs are inaccessible by genomic sequencing tools. Instead, they are almost exclusively analyzed by proteomic technologies. The functional characterization of a PTM event ultimately depends on the unequivocal assignment of the modification site. However, the chemical natures of PTMs are diverse, and many types of PTMs are not amenable to traditional proteomic technologies for site-localization with single amino acid resolution because they are, for example, labile, heterogeneous or low-abundance. We have developed a multidisciplinary program (i.e., chemical biology, quantitative-/chemo-proteomics, computation biology, biochemistry,

molecular biology and animal models) towards the functional analyses of a number of important PTMs, including protein tyrosine sulfation, phosphorylation and Poly-ADP-ribosylation. Besides these naturally occurring PTMs, covalent protein modification has been increasingly appreciated as a novel therapeutic modality. We have also been particularly active in the development of covalent protein modification and chemoproteomic technologies that potentially will revolutionize the principle of drug development by pushing the boundaries of the druggable proteome.

个人简介：

余永豪博士，现任美国哥伦比亚大学 Irving 医学中心分子药理和药物系教授。2001 年毕业于复旦大学化学系。2006 年博士毕业于加州大学伯克利分校， 师从 Julie Leary 教授。之后在哈佛大学医学院 Steven Gygi 和 John Blenis 实验室进行博士后研究。余永豪教授长期从事新颖的蛋白质修饰的发现和功能表征。实验室的优势是利用一系列生化，细胞生物学以及动物模型的手段对这些新修饰的生物调控机制的探索。实验室进而对机理的信息进行转化，开发针对不同疾病(包括癌症，代谢疾病以及神经退行性疾病)的小分子药物和新疗法。获得多个奖项，包括之前的 CPRIT Scholar in Cancer Research 以及 Virginia Murchison Linthicum Scholar in Medical Research. 现任 NIH EBIT (Enabling Bioanalytical and Imaging Technologies) Study Section 评审委员会成员。