

New Frontiers in Proteomics - Proteoforms, Proteoform Families, and the Human Proteoform Project

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Proteins are the primary effectors of function in biology, and thus complete knowledge of their structure and behavior is needed to decipher function. However the richness of protein structure and function goes far beyond the linear amino acid sequence dictated by the genetic code. Multigene families, alternative splicing, coding polymorphisms, and post-translational modifications, work together to create a rich variety of proteoforms, whose chemical diversity is the foundation of the biological complexes and networks that control biology. "Proteoforms" are the specific molecular forms in which proteins are present in biological systems; only direct analysis of the proteoforms themselves can reveal their structures, dynamics, and localizations in biological systems.

Remarkably, the dominant paradigm of proteomics research, "bottom-up" proteomics, does not identify proteoforms –rather, proteins are enzymatically digested into peptides, whose identification then indicates the likely presence of their parent proteins in the sample. This strategy destroys the information as to what form of the protein the peptide represents, and thus the critical information needed to identify proteoforms is lost. The entire field of Biology is thus attempting to understand life in the absence of the ability to understand the molecules that define life. This limitation of today's technology provides a "grand challenge" to the scientific community, to devise new strategies and approaches that are able to comprehensively and quantitatively reveal the full breadth of the proteome at the proteoform level.

In this presentation I will provide an overview of this interesting problem, along with a variety of new tools and approaches that we and others are developing to address it. Developing the technology to decipher proteoforms, building a comprehensive atlas of proteoforms present in human systems, and eventually deciphering the functional roles they play in normal and disease biology, comprise central elements in the quest to understand human biology.

User consent

yes

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