Next-generation proteomics:

towards an integrative view of proteome dynamics

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观念转变：

DNA contains all of the genetic instructions that are necessary to create an organism

genotype and phenotype are not uniquely directed by information that is present on the genome

Epigenetic marks

alternative splicing

non-coding RNAs (including miRNAs)

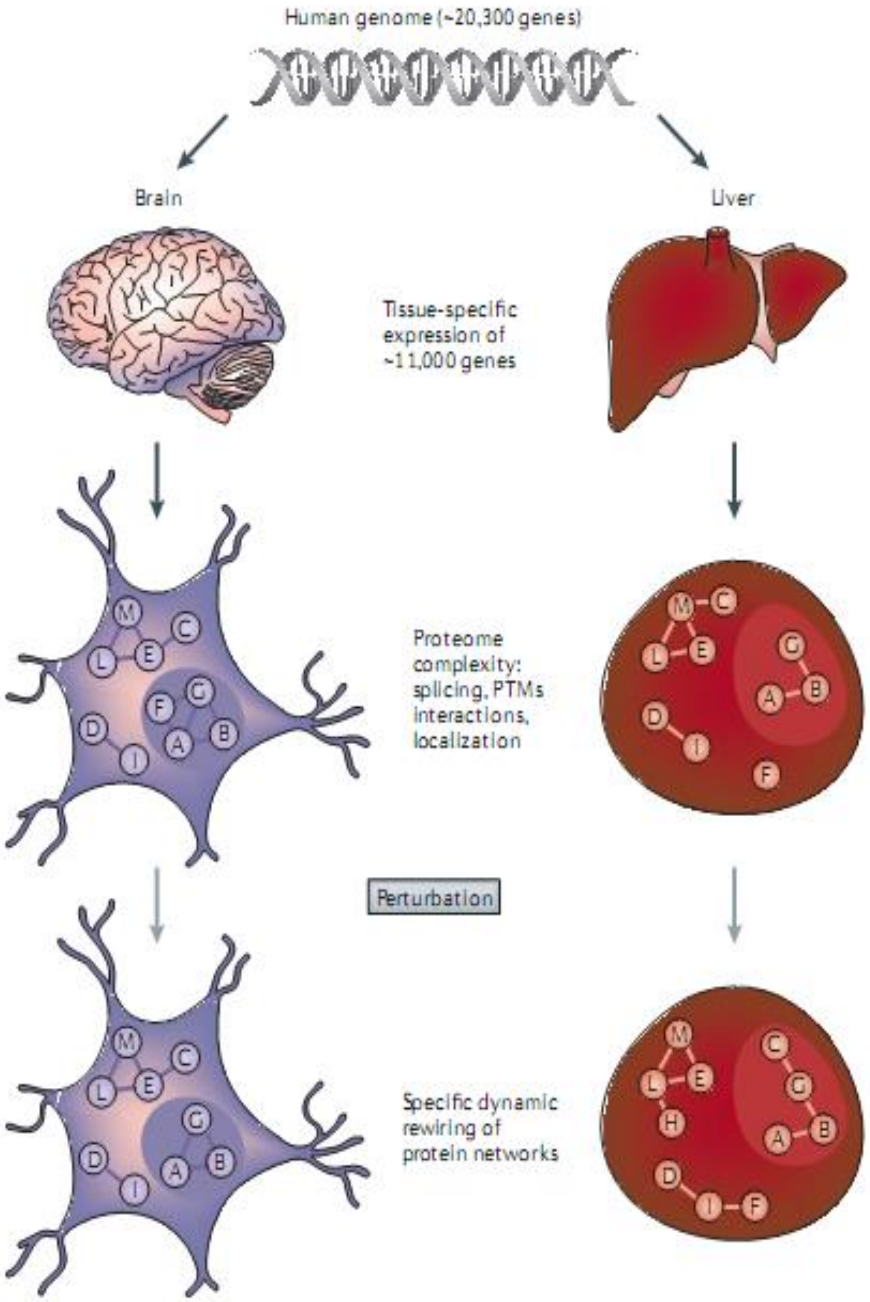
protein–protein interaction (PPI) networks

post-translational modifications (PTMs)

研究背景

the causes of most disorders are multifactorial, and systems-level approaches, including the analysis of proteomes, are required for a more comprehensive understanding.

MS‐based proteomics is starting to mature and to deliver through a combination of developments in instrumentation, sample preparation and computational analysis



The diverse and dynamic mechanisms of proteome regulation provide a higher order of complexity to the human genome.

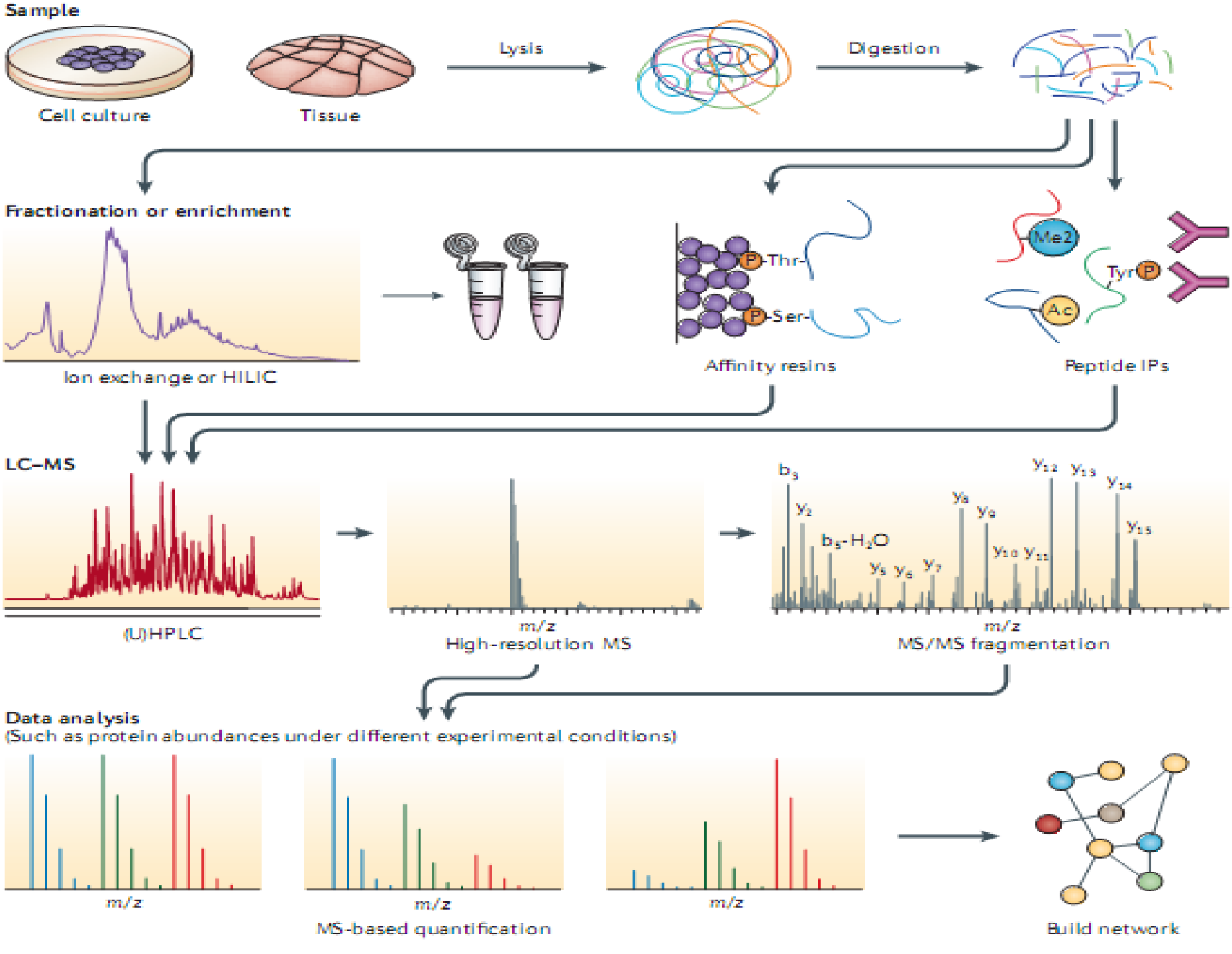
analytical challenge

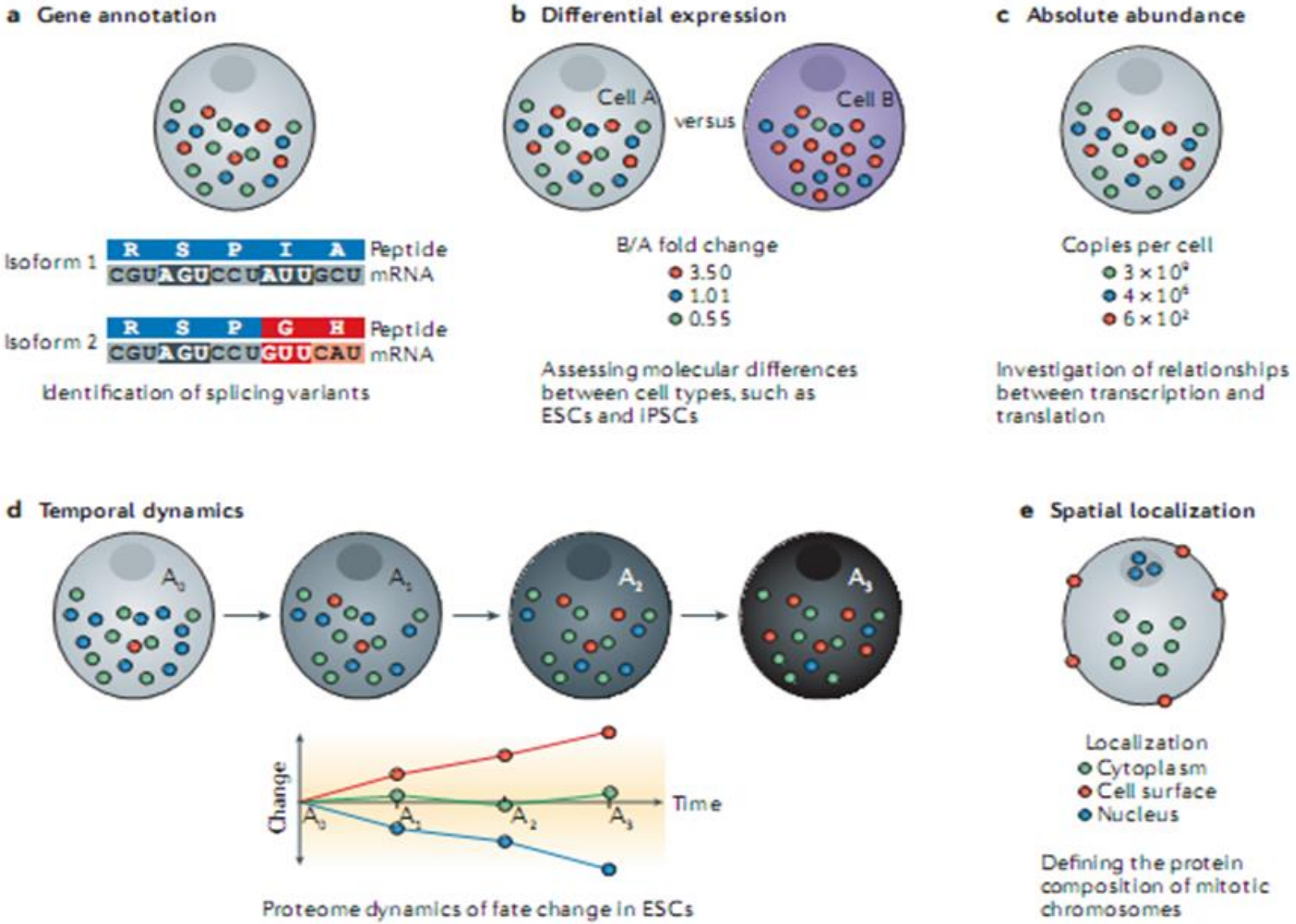
- the highly diverse physicochemical properties of amino acids
- Furthermore, compared to the genome, the proteome is complemented by alternative splicing and diverse protein modifications and degradation
- the interconnectivity of proteins into complexes and signalling networks that are highly divergent in time and space.

- In recent years, proteomics technologies — particularly mass spectrometry (MS)-based protein identification — have matured immensely through cumulative technological advances in instrumentation, sample preparation and computational analysis

实验方法

- 样品裂解，将蛋白质水解为多肽
- 样品分馏或对特定多肽亚群富集
- 逐一进行质谱分析
- 识别相应的肽序列
- 将肽序列组装成蛋白质，并对获得的数据进行统计验证
- 建立蛋白质互作网络

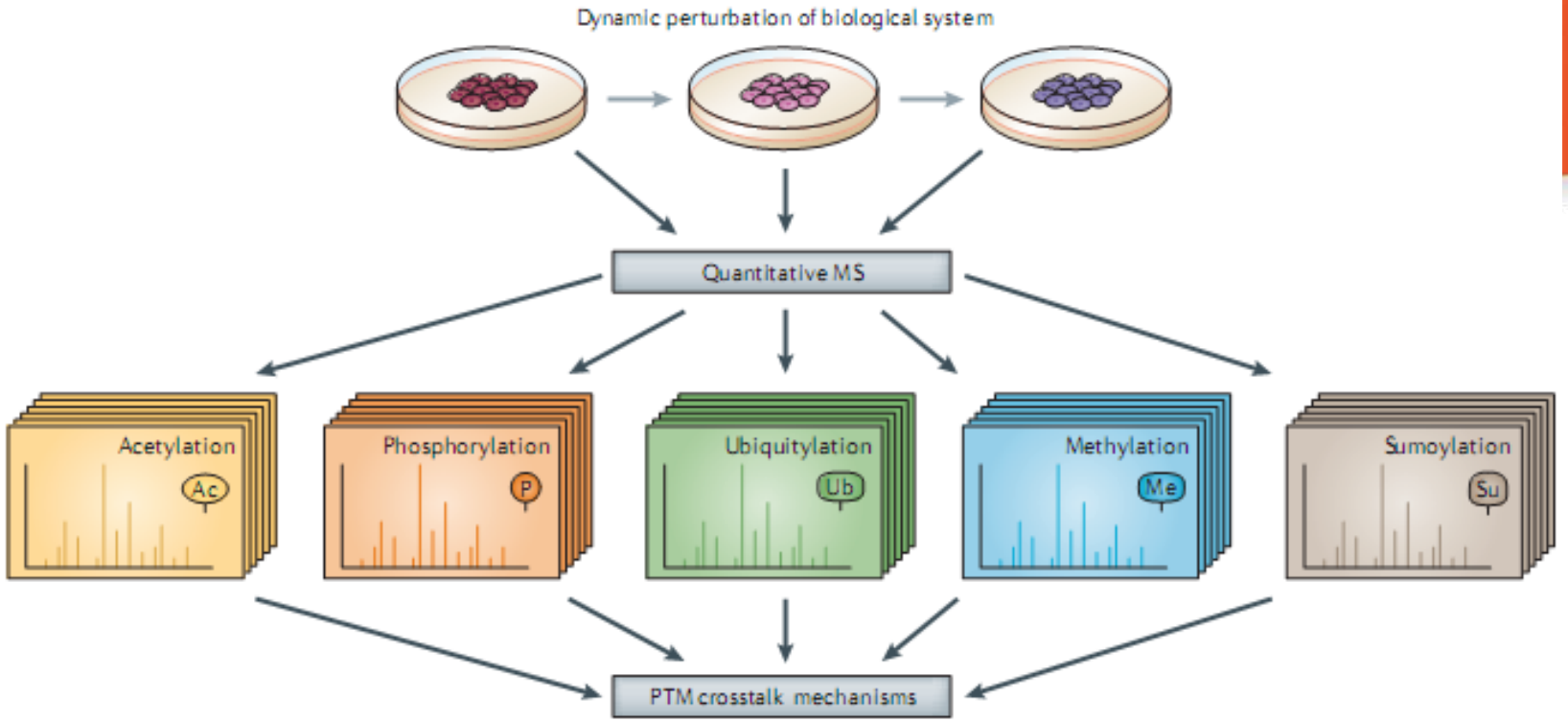

Sample
Cell culture
Tissue
Lysis
Digestion
Fractionation or enrichment
Ion exchange or HILIC
Affinity resins
Peptide IPs
LC–MS
(U)HPLC
m/z
High-resolution MS
m/z
MS/MS fragmentation
Data analysis
(Such as protein abundances under different experimental conditions)
m/z
m/z
MS-based quantification
m/z
Build network

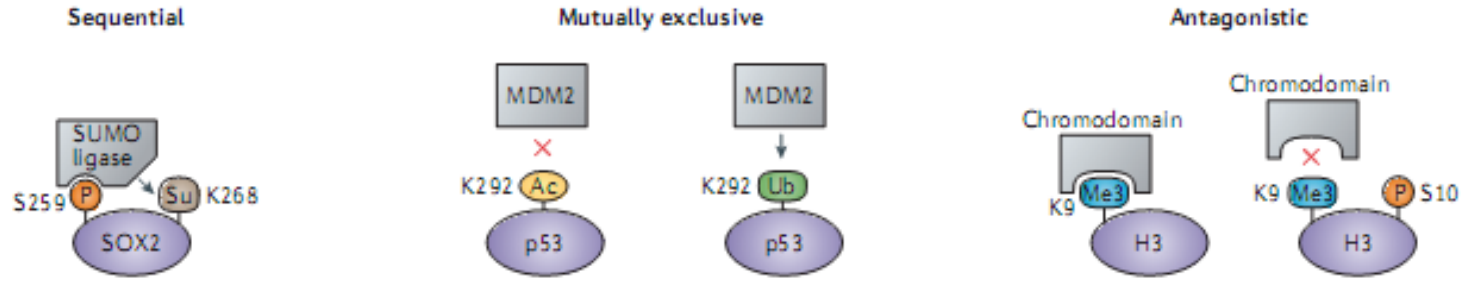


1.基因注释　2.差异表达　3.绝对丰度

4.时间动态变化　　5.空间定位

post-translational modifications





Phosphorylation-dependent SUMO modification

Acetylation prevents degradation of p53 by MDM2

Phosphorylation disrupts H3 interaction with chromodomain

Protein–protein interactions and network biology

- Proteins often interact with each other in stable or transient multi-protein complexes of distinct composition

- proteins can interact with other molecules, such as RNA or metabolites

These complexes have essential roles in regulatory processes, signalling cascades and cellular functions, and loss of the ability to interact can cause loss of function

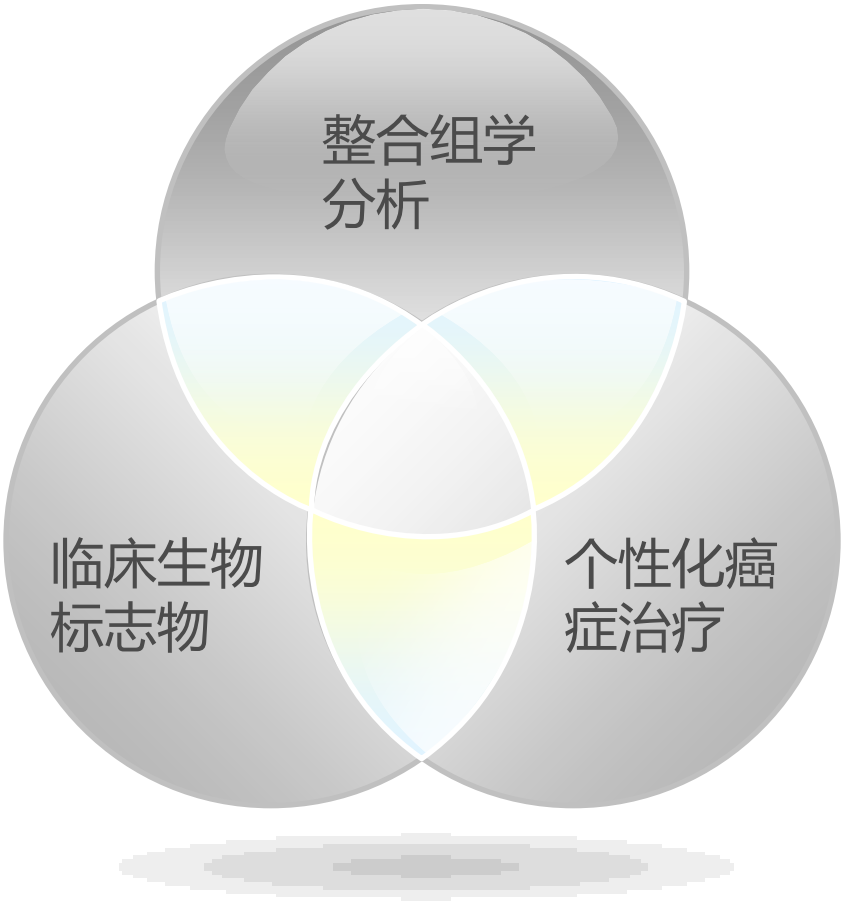
- affinity purification–mass spectrometry（亲和层析质谱法）

  研究蛋白质的相互作用
- Dynamic and quantitative AP–MS

  全局分析，揭示动态蛋白质互作的相关性信息

- 技术挑战：additional developments of computational tools are required that allow modelling of protein network behaviour under changing conditions, as inferred from quantitative AP–MS data

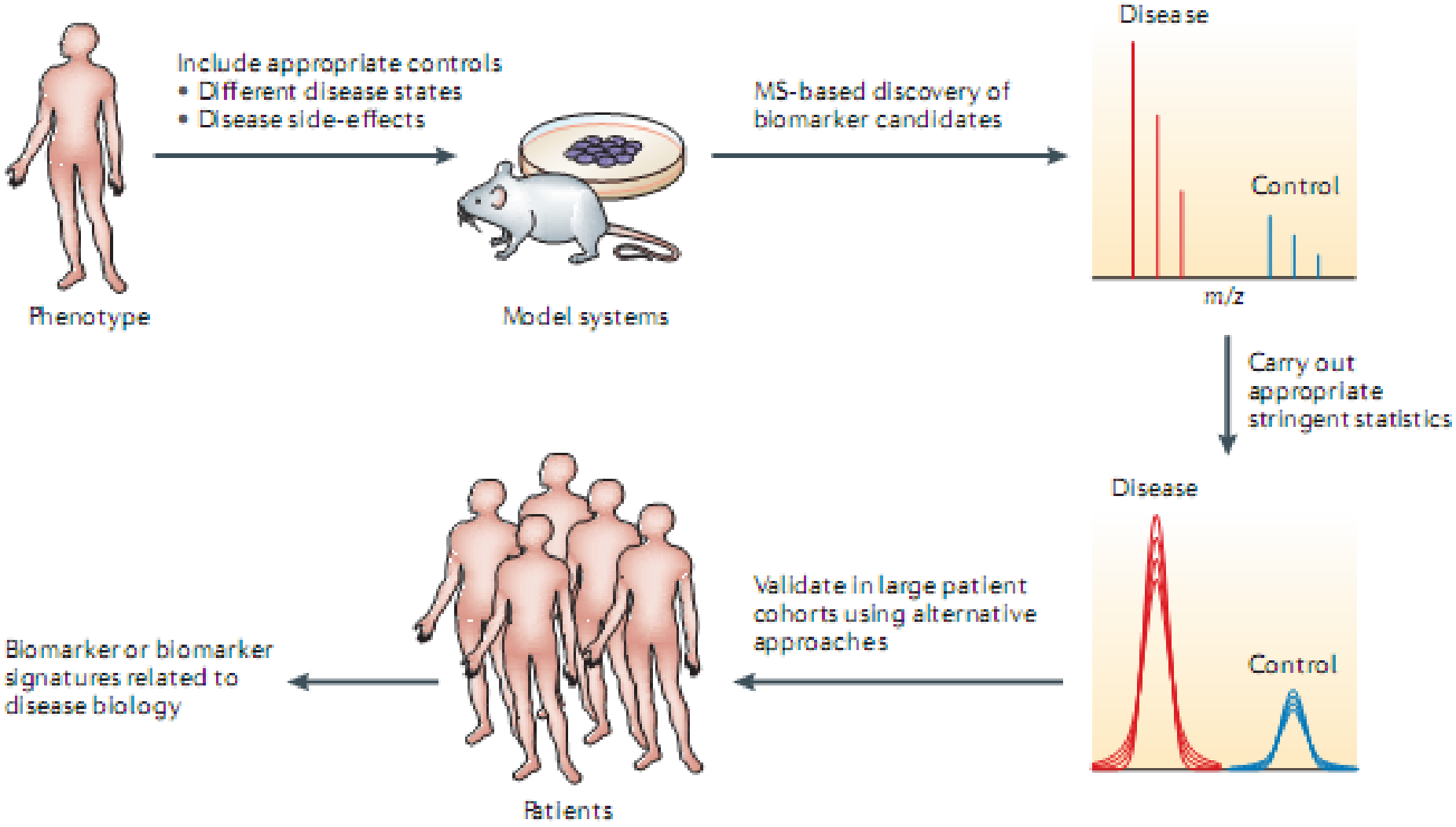
临床应用



整合个人组学揭示医疗风险；癌症治疗中寻找药物耐药性的补救措施

蛋白酶抑制因子；与肺癌相关的蛋白标记物

protein biomarkers



总结

- 下一代蛋白质组学将对全方位的蛋白质组学进行深入研究。作为核心技术，质谱分析将继续在这个竞技大舞台中扮演主要角色。

- 基于质谱分析的蛋白质组学技术将着重于以下三个方面：

1 在更短的分析时间内获取相关的蛋白质组学数据；
2 减少所需材料；
3 深入分析同源细胞群或者显微解剖组织，并以单细胞蛋白质组分析为最终目的。

展望

- 基于质谱分析的蛋白质组学产生的数据具有很强的互补性，对于其他的后基因平台具有独特性，至少在未来十年仍然是被广泛应用的方法。

- 整合生物学方法对于解决系统生物学的问题是必不可少的，常规的整合不仅需要不同的后基因技术的成熟与调整，也需要将不同的学科联系起来。

  所有这些技术的整合最终造成下一代系统生物学的产生，从而提供有意义的生物学见解。

Thanks!