9 Proteomics: high throughput protein functional analysis

Currently, there is a major effort, on a genome-wide scale, to map protein-drug interactions and to discover drug targets (Sect. 9.1), to map protein-protein interactions (Sect. 9.2), to discover chemical activity of proteins (Sect. 9.3), and to resolve protein structures (Sect. 9.5). This effort, called proteomics, provides significant knowledge of the biology of organisms far beyond the level of sequence information (see, e.g., Adam et al., 2002b; Burbaum and Tobal; Edwards et al., 2000, 2002; Christendat et al., 2000; Figeys, 2002a, 2002c; Gallardo et al., 2002; Hubbard, 2002; Kersten et al., 2002; Koshland and Hamadani, 2002; Lin and Cornish, 2002; Liu et al., 2002; Morrison et al., 2002; Natsume et al., 2002; Yarmush and Jayaraman). The system-wide study of proteins and as well non-proteinaceous interaction partners largely employs protein microarray technology (see, e.g., MacBeath, 2002; Gera et al., 2002; Kukar et al., 2002; Talapatra et al., 2002) and bioinformatic methods (see, e.g., Bork, 2002).

Proteomics-based approaches for the study of organ-specific regulatory and signaling cascades are seen as a key for a better understanding and therapeutical management of diseases (e.g., Jäger et al., 2002). Proteomics has provided new vaccine candidate antigens (Klade, 2002; Nilsson, 2002; Vytvytska et al., 2002). The identification of individual proteins abnormally expressed in tumors may have an important relevance for making diagnosis, prognosis, and treatment (e.g., Celis et al., 2002; Dwek and Rawlings, 2002; Jain, 2002; Michener et al. 2002; Zheng et al., 2003). Proteomics analysis of the neurodegeneration in the brain of transgenic mice discovered 34 proteins with significantly changed intensity (Tilleman et al., 2002). A proteomics approach was used to identify the translation products of squid optic lobe synaptosomes (Jimenez et al., 2002). A central nervous system (CNS) proteome database derived from human tissues is expected to significantly accelerate the development of more specific diagnostic and prognostic disease markers as well as new selective therapeutics for CNS disorders (Rohlff and Southan, 2002). Proteomics provides an extremely powerful tool for the study of variations in protein expression between different ages and for the understanding the changes that occur in individuals as they become older (Cobon et al., 2002).

Innovations towards higher throughput and cost cutting include mass spectrometry advances (Sects. 9.1 and 9.2), DNA microchips (Sect. 9.1), protein microchips (Sect. 9.2), genetic hybrid systems (Sect. 9.2), and lab-on-a-chip technology (Sect. 9.4).

9.1 Target discovery

Two-dimensional electrophoresis and mass spectrometry (Fig. 9.1) are widely used for the study of protein composition and protein changes in humans, animals, and plants. Important applications are (a) the identification of biomarkers specific for certain cell types, disease states, or aging processes, and (b) the study of protein composition changes as a response to drug treatment.

Also, high throughput microarray-based assays hold tremendous promise for the discovery of proteins connected with diseases (Fig. 9.2).

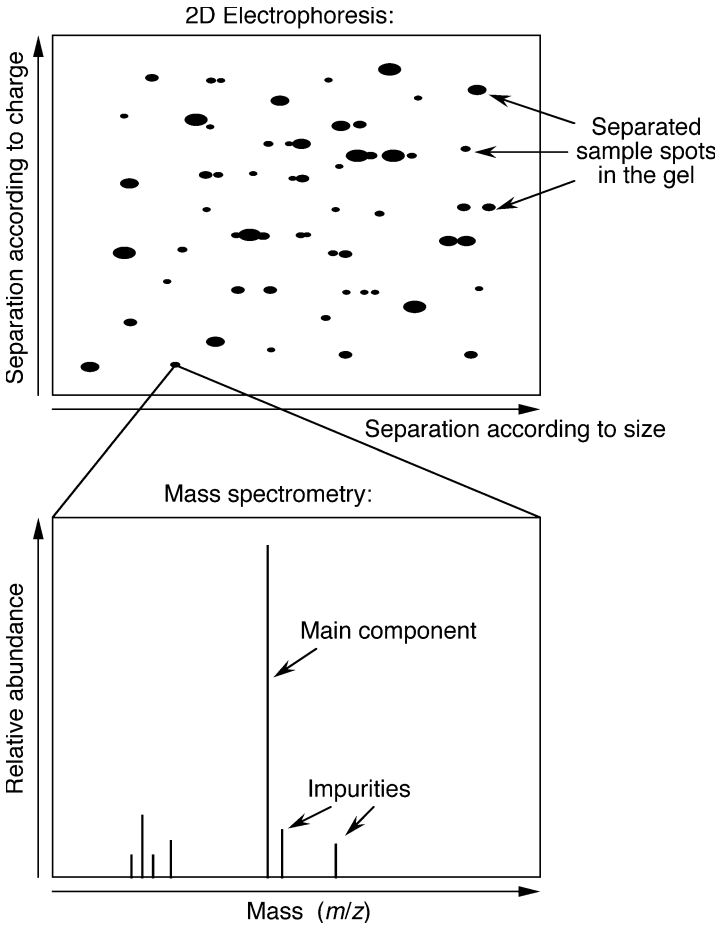

Fig. 9.1 Discovery of proteins relevant to a certain disease by two-dimensional polyacrylamide gel electrophoresis and mass spectrometry (see, e.g., Edwards et al., 2000; Blomberg, 2002; Kersten et al., 2002; Man et al., 2002; Mo and Karger, 2002; Rohlff and Southan, 2002)