Glycomics and Lipidopics

Extended Abstract

# Cellulose membranes are more effective in holding back vital proteins and exhibit less interaction with plasma proteins during hemodialysis

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**Abstract:**

The vast majority of patients with end-stage renal disease are treated with intermittent hemodialysis as a form of renal replacement therapy. To investigate the impact of hemodialysis membrane material on vital protein removal, dialysates from 26 well-characterized haemodialysis patients were collected 5 min after beginning, during 5 h of treatment, as well as 5 min before ending of the dialysis sessions. Dialysis sessions were performed using either modified cellulose (n=12) (low-flux and high flux) or synthetic Polyflux (n=14) (low-flux and high-flux) dialyzer. Protein removal during hemodialysis was quantified and the dialysate proteome patterns were analyzed by 2-DE-MS and Western blot. There was a clear correlation between the type of membrane material and the amount of protein removed. Synthetic Poly flux membranes exhibit strong interaction with plasma proteins resulting in a significantly higher protein loss compared to modified cellulosic membrane. Moreover, the proteomics analysis showed that the removed proteins represented different molecular weight range and different functional groups: transport proteins, protease inhibitors, proteins with role in immune response and regulations, constructive proteins and as a part of HLA immune complex. The effect of this protein removal on hemodialysis treatment outcome should be investigated in further studies. Uremia is a clinical syndrome resembling systemic poisoning , characterized by a variety of clinical symptoms that develop and worsen as kidney failure proceeds, due to the retention of various solutes, which are normally excreted by the kidney, called uremic toxins. The principal aim of renal replacement therapies is the removal of uremic toxins, targeted at an improvement in quality of life and survival. Hemodialysis (HD) is by far the most commonly used modality for chronic renal replacement: more than 1.7 million patients are currently treated with HD worldwide, a number that is growing at a rate of approximately six-to-seven percent annually. In the extracorporeal HD system, blood is allowed to flow via a peristaltic pump into a special filter (hemodialyzer) whereby waste products and excess water are removed across a semipermeable membrane separating flowing blood from the dialysate stream; the cleaned blood is then returned to the patient's body, while wastes are discharged. The main determinant of the success and the quality of HD therapy is represented by the artificial membrane packed into the hemodialyzers. Membranes are thin barriers capable of providing the removal of substances between adjacent phases, so that chemical and biophysical control consistent with continued survival is achieved. Moreover, protein adsorption following the contact of blood with the membrane material during the HD procedure is vital to the bio(in)compatibility of a membrane material, a justifiable concern in dialysis. Today, most membrane materials follow the concept of first generation biocompatible materials. In these biomaterials the engineering aims to achieve an appropriate combination of chemical and physical properties, which may be useful in replacing the basic function of the original tissue with a minimal response in the host. Second generation materials, as defined by HD procedure associated with bioactive components in order to elicit a specific biological response at the interface of the material, are currently being developed by combining biochemically active compounds such as vitamin E to scavenge oxygen reactive species. Although these materials provide a fundamental therapeutic technology for end-stage renal disease (ESRD) patients, they are still far from developing a precision healthcare approach dedicated to the specific physiopathological conditions of different individuals. As such, third and fourth generations biomaterials are not currently available in renal replacement therapies. To develop such membranes requires the collection of basic primitive systematic evidence that proteomic investigations may provide. Proteomic investigations enable analysis of complex multivariate protein functional mechanisms in a defined biochemical experimental model, and can be performed either as unsupervised or as targeted analysis. Application of proteomics has become one of the leading technologies for increased understanding of the key role played by proteins and protein–protein interactions in all aspects of cell function. There is an increasing use of proteomic technologies for investigation into renal replacement therapy such as HD . In the last 10 years, the application of 2 dimensional electrophoresis (DE) separation techniques has been almost completely substituted by the use of shotgun

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bottom-up liquid chromatography (LC)-mass spectrometry (MS)/MS approaches. These analyses are more convenient and reproducible, however they provide molecular information at the peptide level only, thus subtle definition of specific protein isoforms available in the 2DE is often missing. More recently, the definition of top-down strategies in high resolution LC-MS/MS experimental set up is providing a new ground to define the specific proteoforms and their tentative association with specific biological states. These newly developed MS techniques have been successfully applied to research in uremic toxicity, with the discovery of novel uremic toxins and the potential to define a precise molecular approach to defining the biochemical nature of uremia. Proteomic investigations associate genomic information with functional insight into the mechanisms involved in the interactions between the artificial membrane material and blood, thus providing the basic knowledge for generation of third-generation HD biomaterials. Moreover, to develop new concepts in the engineering of smart-biomaterials—fourth generation materials that may mimic nature's hierarchical structural assemblages providing a framework to underpin the spatial and temporal relationships of molecular events during the life span of a patient—will necessarily require the collection of proteomic data. In fact new multifactorial molecular evidence will be needed if we are to achieve the complexity necessary to mimic natural tissues. In this article, we review the results of recent proteomic investigations in the setting of chronic HD therapy. Studies of uremic solute removal tend to segregate into biological mechanisms, clinical associations and dialyzer kinetics. To date, more than 115 uremic toxins have been identified, and more are expected. Two main points about uremic toxins and research into them emerged and have been highlighted in a recent paper: (i) the importance of a standardized approach to testing the biologic effect of uremic retention solutes, using appropriate concentrations and control conditions, taking into account (especially for protein-bound solutes) the albumin content of the test medium, and excluding confounding factors like contamination by bacterial derivatives; (ii) that the strength of the biological effect of uremic retention solutes is related to their concentration, which is affected not only by dialysis removal but also by endogenous metabolism generation, especially for the small water-soluble compounds such as the guanidine compounds or the purines, and the middle molecules. Some molecules, like the advanced glycation end products (AGEs), are present in food and absorbed unmodified, whereas several protein-bound solutes and volatile compounds are metabolites produced by the natural digestion process , then transformed by the intestinal wall or the liver via conjugation . For example, tyrosine is modified by the intestinal microbiota into *p*-cresol, to be further metabolized in the body to *p*-cresylsulfate and *p*-cresylglucuronide . This further indicates the complexity of uremic toxicity and its biological/biochemical environment.

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