Design and use of silica-containing redox nanoparticles, siRNP, for protection of encapsulating peritoneal sclerosis

Yukio Nagasaki¹, Tatsuya Yaguchi¹, Takuma Matsumura¹, Toru Yoshitomi¹, Yutaka Ikeda¹, Atsushi Ueda², and Aki Hirayama³

¹Department of Materials Science, Master’s School of Medical Sciences, and Satellite Laboratory, International Center for Materials Nanoarchitectonics (WPI-MANA), National Institute for Materials Science (NIMS), University of Tsukuba, Tennoudai 1-1-1, Tsukuba 305-8573, Japan, ²Tsukuba University Hospital Hitachi Medical Education and Research Center, Jyonan-chou 2-1-1 Hitachi Ibaraki 317-0077, Japan, ³Center for Integrative Medicine, Tsukuba University of Technology, Kasuga 4-12-7, Tsukuba 305-8521, Japan; yukio@nagalabo.jp

ABSTRACT SUMMARY
The prevention of encapsulating peritoneal sclerosis (EPS) and enhancement of dialysis efficiency are two important strategies that can improve the quality of life of patients undergoing peritoneal dialysis. We have thus far developed bionanoparticles that effectively scavenge reactive oxygen species (redox nanoparticles; RNP). The objective of this study was to apply RNPs as a component of dialysate to reduce oxidative stress. Porous silica nanoparticles were combined with RNPs to enhance the effective adsorption capacity of low-molecular weight (LMW) compounds. The silica-containing RNPs (siRNPs) were confirmed to statistically decrease the level of creatinine and blood urea nitrogen in vivo. EPS model rats that underwent intraperitoneal injection of chlorhexidine gluconate exhibited dysfunction of the peritonitis. No blood uptake of siRNPs was observed when they were administered into the peritoneal cavity. Considering these results, siRNPs are expected to be a new multi-functional nanomaterial for high performance peritoneal dialysis (PD). Although HD substitutes for a portion of renal function, there still remains several issues such as: 1) The continuous need for hospital attendance, which limit the social activities of patients; 2) insufficient removal of medium molecular weight uremic toxins; and 3) the removal of body fluid in a short time thereby leading to cardiac overload and vascular damage. These issues increase in terms of patient risk for several serious diseases such as stroke and myocardial infarction. In contrast, the following reasons make PD the first choice of RRT in many countries: 1) Low load in terms of medical economies; 2) social precedence during domiciliary treatment; and 3) medical advantages with respect to patient outcome. For the last reason in particular, current studies are successively revealing the advantages of PD-first policy as they relate to residual renal function and survival rates. For example, dialysate can be changed by oneself. In addition, rehabilitation is easy, it maintains renal function, and the risk of stroke and myocardial dysfunction is low. Thus, PD has much potential to provide high quality of life to patients who are undergoing RRT.

INTRODUCTION
Recently, technological developments in renal replacement therapy (RRT) have been used to successfully treat patients with renal failure. By the end of 2010, 2.03 million patients were undergoing RRT. Nearly 90% of these patients received hemodialysis (HD) therapy, while worldwide only 8.4–11% were treated with peritoneal dialysis (PD). Although HD substitutes for a portion of renal function, there still remains several issues such as: 1) The continuous need for hospital attendance, which limit the social activities of patients; 2) insufficient removal of medium molecular weight uremic toxins; and 3) the removal of body fluid in a short time thereby leading to cardiac overload and vascular damage. These issues increase in terms of patient risk for several serious diseases such as stroke and myocardial infarction. In contrast, the following reasons make PD the first choice of RRT in many countries: 1) Low load in terms of medical economies; 2) social precedence during domiciliary treatment; and 3) medical advantages with respect to patient outcome. For the last reason in particular, current studies are successively revealing the advantages of PD-first policy as they relate to residual renal function and survival rates. For example, dialysate can be changed by oneself. In addition, rehabilitation is easy, it maintains renal function, and the risk of stroke and myocardial dysfunction is low. Thus, PD has much potential to provide high quality of life to patients who are undergoing RRT.

However, the long-term outcome of PD is...
still poorer than that of HD. Two major reasons for this are: 1) The insufficiency of dialysis due to loss of peritoneal function, which thus increases changes in dialysate; and 2) the occurrence of encapsulating peritoneal sclerosis (EPS), which is a fatal complication of PD. Chronic inflammation of peritoneal membrane leads to encapsulation of the intestine, which then results in severe ileus and malnutrition in EPS patients. Dialysate with a high glucose concentration causes oxidative stress to the peritoneum and results in EPS over the course of several years. Frequent changes in dialysate increase the risk of contracting infectious diseases. Resolving these would not only increase the quality of life for the patient, but also reduce medical costs worldwide. For these objectives to be met, both a decrease in oxidative stress to the peritoneal membrane and an increase in the adsorption capacity of blood wastes are required.

RESULTS AND DISCUSSION

We have previously developed novel nanotherapeutics with redox nanoparticles (RNPs) containing nitroxide radicals as free radical scavengers for treating cerebral and renal ischemia-reperfusion, as well as brain hemorrhage. Typical characteristics of RNPs are: 1) Because nitroxide radicals are covalently conjugated to the nanoparticle backbone, they are not leaked to the outside of the nanoparticle; 2) the sizes of RNPs are ca. 40 nm in diameter and thus they are not internalized into healthy cells; and iii) as a consequence RNPs do not interfere with normal redox reactions inside of cell. These characteristics help RNPs selectively scavenge over-produced reactive oxygen species (ROS), especially outside of the cell. We have so far confirmed the therapeutic effects of RNPs with respect to several disease models such as cerebral and renal ischemia reperfusion injuries, cerebral hemorrhage, cancer, ulcerative colitis, and small intestinal inflammation.

The objective of this study was to apply RNPs as one of the components in dialysate to reduce oxidative stress. Porous silica nanoparticles were combined with RNPs in order to enhance the adsorption capacity of creatinine and other LMW compounds effectively (Fig. 1). The silica-containing RNPs (siRNPs) thus prepared were confirmed to increase the adsorption capacity of uremic toxins in vivo (Fig. 2). EPS model rats were prepared by injecting them daily with chlorhexidine gluconate (CH) intraperitoneally (i.p.) for a week. siRNPs was administered to the peritoneal cavity of the rats at the same time to confirm that they were protected against CH-induced inflammation (Fig. 1). CH-induced dysfunction of peritonitis such as disruption of the mesothelial cell layer and vascularity of the expanded submesothelial compact zone was not observed for the siRNPs treatments. These results show potential for siRNPs to be used as a new multi-functional nanomaterial in peritoneal dialysis.

CONCLUSION

We have designed and developed a siRNP for treatment of EPS caused by peritoneal dialysis, reducing ureic toxins effectively. Our study indicates that the siRNP system is an innovative therapeutic material for the treatment of peritoneal dialysis.

REFERENCES


**Fig. 2.** Therapeutic effect of silica-containing redox nanoparticles (siRNPs(2)) as an additive of peritoneal dialysis (PD)-dialysate against renal failure model mice. Vehicle: 2.4 mL of 4.25 w/v% glucose solution; RNP: 2.4 mL of 4.25 w/v% glucose solution containing RNPs 100 mg/mL and siRNPs(2): 2.4 mL of 4.25 w/v% glucose solution containing siRNPs(2) 100 mg/mL for 6 h (a) and 9 h (b). *p < 0.05; **p < 0.01; ***p < 0.005