

外国語要旨

Anticancer agent PSK and therapeutic agent for chronic kidney disease AST-120

- A study on the new effects and their mechanisms of action -

Rieko Aoki

Diseases, the onset and progression of which are associated with the lifestyle habits; i.e. eating, exercise and smoking, etc; are generically called lifestyle-related diseases. The lifestyle-related diseases include not only three major causes of death in Japanese people, which are cancer, cerebrovascular disease and heart disease, but also arteriosclerosis, diabetes, hypertension, renal disease and etc.. Recently with the westernization of eating habits, the number of patients of lifestyle-related diseases has increased, accounting for about 60% of the number of deaths. Therefore, the prevention and treatment methods for these diseases are sought. This paper will report on the new effects and mechanisms of action of anticancer agent PSK and therapeutic agent for chronic kidney disease AST-120 by focusing on cancer and diabetic nephropathy.

1. Effect of PSK on Regulatory T cells

Regulatory T cells (Tregs) play an important role in maintaining immunological tolerance. However this mechanism is one of the major obstacles to overcome when trying to improve antitumor immunity. PSK has been used clinically as an antitumor drug, and one of its anti-tumor mechanisms is in improving a tumor-induced immunosuppressive state. Therefore, we investigated whether PSK affects Tregs in vitro and in vivo. In the in vitro study, CD4+CD25- cells were separated from normal mouse spleen and cultured with or without PSK in the presence of TGF β . Although TGF β induced CD4+CD25+Foxp3+ Tregs, PSK reduced the proportion of TGF β -induced Tregs. In the in vivo study, BALB/c mice were injected subcutaneously with methylcholanthrene-induced fibrosarcoma (Meth A) cells on day 0, and administered PSK 50 mg/kg intraperitoneally from day 1, three times per week. After 4 weeks, the tumor volume, the proportion of Tregs and the CD8+/Tregs ratio in spleen, plasma TGF β concentration, and IFN γ production by spleen cells were measured. PSK significantly reduced tumor growth, proportion of Tregs in spleen and plasma TGF β concentration, and significantly increased the CD8+/Tregs ratio in spleen and IFN γ production by spleen cells. The reduction of TGF β concentration in blood by PSK may decrease the proportion of Tregs in lymphoid organs and augment antitumor immunity.

2. Effect of an Oral Adsorbent AST-120 on Proteinuria, Albuminuria and podocyte injury in Metabolic Syndrome/Diabetes Rats

Diabetic nephropathy is a major complication of diabetes and the leading cause of end-stage renal

disease. An oral adsorbent AST-120 has been used clinically as a medicine for patients with chronic kidney disease to slow down the progression of it. However, there is little evidence to support therapeutic efficacy of AST-120 for early stage overt diabetic nephropathy. In this study, we aimed to assess the effect of AST-120 on SHR/NDmcr-cp rats, model rats of type 2 diabetes / metabolic syndrome. Male SHR/NDmcr-cp (SHR/ND) rats were divided into two groups. One group was administered 0% and the other group was administered 8% of AST-120 for 12 weeks in their diets. At every 4 weeks, serum and 24-hour urine samples were collected for biomedical studies. We examined the oxidative stress and podocyte injury. We also investigated the dose-response effect of AST-120. 8% AST-120-administered SHR/ND rats showed significantly lower levels of urinary protein excretion, urinary albumin excretion, urinary 8-OHdG, urinary podocalyxin excretion and FPW compared to the unadministered SHR/ND rats. The FPW was significantly correlated with the levels of urinary protein excretion ($r = 0.950$) and urinary albumin excretion ($r = 0.953$). AST-120 reduced the urinary protein excretion and urinary albumin excretion in a dose-dependent manner. The amelioration of podocyte injury by AST-120 may contribute to the reduction of proteinuria and albuminuria. These results indicate that the administration of AST-120 at an early stage of diabetic nephropathy would be beneficial to protect from the disease progression.

Finally, the new mechanisms of action in PSK and AST-120 may be contributing to people's health.