TH1-Oriented Immunomodulating Activity of Gel-Forming (1→3)-ß-Glucan

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Several (1→3)-branched (1→3)-β-D-glucans (β-glucans) from mushrooms are known to enhance various immunopharmacological activities such as antitumor activity. Some of them, including lentinan and sonifilan (SFG), have been used clinically for cancer therapy in Japan. We have been investigating various immunopharmacological effects of β-glucans, such as grifolan (GRN) from *Grifola frondasa* (Dicks.: Fr.) S. F. Gray and sclerotinia sclerotiorum glucan (SSG) from *Sclerotinia sclerotiorum* IFO 9395, which were isolated originally by our group. GRN has a similar primary structure to SPG, but SSG consists of β-(1→3)-polyglucose backbone with every second residue substituted with monoglucosyl branches. The ultrastructures of GRN and SSG are distinct from that of SPG. Namely, GRN and SSG contain a mixture of single and triple helix conformers, whereas SPG is composed of triple helixes only. Using SPG and SPG-OH, which is a single helical conformer prepared by alkaline treatment of SPG, we also found previously that the biological activities of β-glucans, that is, blood clearance, reactivity of limulus factor G activation, and nitric oxide (NO) synthesis *in vivo* and *in vitro*, are strongly associated with their conformation. However, we do not yet know the details of activities of various β-glucans on helper T-cell modulation.

The immunomodulating effects of various gel-forming (1→3)-β-glucans on balancing helper T-cell activity were examined in a murine model. Plasma from mice that were injected with GRN or SPG-OH and trinitrophenyl ovalbumin (TNP-OVA) contained TNP-specific antibodies of both IgG1 (Th2-mediated) and IgG2a (Th1-mediated) isotypes. Administration of SSG and TNP-OVA significantly augmented the synthesis of IgG2a antibodies, while the synthesis of IgG1 was reduced. However, SPG did not enhance the antibody response. Furthermore, it was shown by intracellular cytokine staining that the proportion of interferon-γ (IFN-γ)$^+$CD4$^+$ double-positive cells among the CD4$^+$ cells from mice administered with SSG was most strongly increased by addition of PMA and A23187. On the other hand, the expression of IL-12 p40 mRNA was more markedly elevated in splenocytes after combined administration of TNP-OVA plus SSG than after administration of TNP-OVA alone. The highest IFN-γ production was observed when adherent cells of mice administered TNP-OVA and SSG were cultured with TNP-primed lymphocytes. This effect of administration of SSG on IFN-γ production was completely inhibited by addition of anti-IL-12 mAb. In conclusion, our study showed that β-glucans have various effects on the Th1- or Th2-dependent antibody subclasses; in particular, SSG induces the development of Th1 cells via the interleukin-12 (IL-12) pathway.

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