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CHARACTERISTICS OF THE GROWTH HORMONE-LIKE FACTOR PRODUCED BY PLEROCERCOIDS OF *SPIROMETRA ERINACEI*

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Parasites are essentially pathogenic organisms that injure organs of the host with mechanical and chemical irritations and disturb its development by taking nutrients from the host. However, parasites lose own lives when they kill their host. Therefore, they have to adjust effectively to their host, evading immunological attacks from the host. Although plerocercoids of the tapeworm, genus *Spirometra*, infect both man and domestic animals and cause important zoonoses, this is not why these organisms are noteworthy. Plerocercoids have been noticed because of their ability to produce and release a substance which binds and activates growth hormone (GH) receptors, resulting in accelerated growth of the host.

Spirometra erinacei is the only species of *Spirometra* found in Japan and infects domestic and wild cats and dogs as well as racoon dogs. Plerocercoids are able to infect species of all classes of vertebrates except fish. The mice, including Snell dwarf mice, hypothyroid mice and streptozotocin diabetic mice, which were infected with plerocercoids had accelerated growth with an increase in the number of the infected plerocercoids. Plerocercoid infection stimulated the incorporation of ³H-thymidine or ³⁵S-sulfate in costal cartilages of Snell dwarf mice, resulting in the proliferation of the cartilage. On the contrary, plerocercoids decreased in the GH content in the hypophysis and the thyroxine and triiodothyronine levels in the serum of normal mice. Furthermore, the serum from plerocercoid-infected mice increased in the incorporation of ³H-thymidine in cultured mouse parenchymal hepatocytes. On the other hand, the extract of plerocercoids displaced ¹²⁵I-human GH from its receptor on hepatic membranes prepared from a pregnant rabbit. Therefore, the substance produced by plerocercoids, plerocercoid growth factor (PGF), was considered to mimic the physiological actions of GH in the host. The PGF was purified from the extract of plerocercoids as 27 kDa protein, using GH receptor-affinity chromatography and gel filtration, and then cross-reacted against anti-human GH monoclonal antibody. In addition, a partial amino acid sequence of this protein showed the homology of 67% to cysteine proteinase. The addition of this 27 kDa protein stimulated proliferation of the cultured mouse parenchymal hepatocytes and the ability of this protein was inhibited by the addition of E64 which was a specific cysteine proteinase inhibitor.

Furthermore, this 27 kDa protein cleaved human IgG and then the worm extract containing this protein also cleaved anti-27 kDa rabbit polyclonal antibody. Using the monoclonal antibody directed against PGF, PGF was present extensively on the external surface of the tegument and in the tegumental cells of plerocercoids. Therefore, it appears that plerocercoids coat themselves with this proteinase and its most important function is to penetrate tissues for invasion into their hosts.

On the other hand, the incubation media of plerocercoids induced the expression of IL-1, IL-6 and TNF- α mRNA and suppressed the LPS-induced expression of IL-6, TNF- α and inducible nitric oxide synthase (iNOS) mRNA in mouse peritoneal macrophages. The factors, which induced or suppressed these mRNA in peritoneal macrophages, were partially purified by gel filtration and anion exchange chromatography and consisted of two substances in the incubation media.

In conclusion, PGF and other physiologically active factors produced by plerocercoids may be an effective aid in the invasion of hosts and evasion of their immune response by a combination of proteolytic cleavage of IgG attached to the surface of plerocercoids and inactivation of the immune system associated with functions of macrophages.

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