Inactivation and Lysis of Oncornaviruses by Human and Primate Complement

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Oncornavirus genomes, viral antigens and infectious viruses have been shown to be present in malignant and normal tissues and sera of many animal species including avian, murine, feline, bovine, ovine and recently primates by molecular hybridization, immunologically and by virus isolations. To date, there is no clear evidence of isolation or the presence of oncornaviruses in man. The long history of failures to isolate oncornaviruses from human leukemias and sarcomas, indicates that these viruses do not play a prominent role in these malignancies. Although oncornaviruses are antigenic in man, at least Rauscher murine leukemia virus, antibodies to viral antigens, have only infrequently been found in serum of patients with leukemias and in normal individuals. However, as many negative results have been reported, using same techniques for antibodies detection i.e., radio immuno assays.

As prèviously reported (Welsh, 1975; Cooper, 1976; Gallagher, 1978; Sherwin, 1978) human and primate sera, inactivates murine, feline, simian, and avian oncornaviruses, heated human (56° for 30′) or fresh guinea pig, rabbit, rat, bovine or murine sera had no effect.

Heated human or primate sera plus guinea pig complement were equally ineffective. The inactivation of oncornaviruses was antibodies-independent and the mechanism of inactivation was by viral lysis, since the internal enzyme, RNA dependent DNA polymerase and viral RNA were released after incubation.

Inactivation was complement-dependent, as heated human or heated primate sera, or C2, C4 or C8-deficient human sera did not produce viral lysis. When purified C2, C4, or C8 were added to deficient human sera, virolytic activity has been restored.

The C1Q subunit of the first human C component attaches directly to the oncornavirus envelope in the absence of immunoglobulin binding of C1. CIQ leads to activation of C1 and thus of the classical C pathway, accompanied by deposition of C components on the viral envelope and lysis on completion of complement sequence.

Recently Gallagher et al. and Sherwin et al. reported and confirmed our previous observations of complement mediated lysis of oncornaviruses by human and primate sera. Although the gibbons are unusual among the primates that they are so susceptible to horizontal infection with oncornaviruses in captivity. As shown by Gallagher et al., only the viremic gibbon had no detectable serum lytic activity. A normal adult gibbon had serum lytic activ-

ity, before and after deliberate inoculation with gibbon ape leukemia virus. Post inoculation, this gibbon was not viremic, developed antibodies within three weeks post-inoculation and has remained healthy. It is possible, that during the early period of captivity, the gibbons are exposed to many viral, bacterial and mycotic infections. Such infections could affect the compliment levels and make them susceptible to infection with oncornaviruses of Mus caroli or Mus cervicolor as reported by Todaro et al.

Leukemias and lymphomas among primates are rare and there are few reported cases in the literature. In an outbreak of spontaneous malignant lymphoma in rhesus monkeys (45/450) at the California Primate Research Center at the University of California in Davis, oncornaviruses were not isolated and not seen by electron microscopic examination of malignant cells (Takemoto, H., Pers. Communication).

In collaboration with Drs. Russell and Vanderlip, we tried to isolate oncornaviruses from a male adult baboon (Papio papio) who developed an osteosarcoma of the mandibule. Cultures were established from tumor and from normal tissues. Oncornaviruses were not isolated from the tumor nor from long term cultures of normal tissues and are still free of C type viruses 24 months in continuous cultivation. Electron microscopic examination of the osteosarcoma and of kidneys, lungs, brain, epidydimus, testes, and lymphnodes were negative for C type viruses. Although as shown by Benveniste and Todaro the baboons have multiple oncornavirus gene copies in their DNA. However, the virus is under strict cellular control and only seldom expressed. There is no evidence to date that oncornaviruses of baboons are horizontally transmitted in nature. It is of interest that majority of the isolates from human leukemias are identical to C type virus isolate M-7 from Papio cynocephalus, which has been distributed to several laboratories. In laboratories where M-7 was not used experimentally, cell cultures from other laboratories were obtained, which could have been infected with M-7.

The fact that all the so called human isolates from leukemic and normal human embryonic tissues are identical to M-7 isolate, deserves great caution. As shown by Benveniste and Todaro the three different isolates from baboon subspecies: Papio cynocephalus, P. hamadryas and P. papio differ from each other by molecular hybridization. There were other excellent markers in the 27000 Dalton protein which we have established in our laboratory (Gautsch et al., 1978) which confirm the identity of the so-called "human" isolates. For the record, I would like to state that in species where C type viruses are horizontally spread, such as gibbons, feline, bovine, and equine, antibodies to all viral peptides are readily demonstrated by several immunological tests and these results are in full agreement between the various laboratories around the world.

Lysis of oncornaviruses by human and primate complement is of major immunological importance as a defense mechanism against horizontal infection. Since humans are in close contact with viremic cats the virolytic activity of complement might be responsible as to why infection with these viruses doesn't occur.

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