Potential Leukemia Virus Subunit Vaccines: Discussion

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Most if not all well-studied leukemias in the chicken, mouse, and cat are associated with a replicating C-type virus. In these animal models the interaction between the virus and the target cell can be very specific, i.e., a particular virus strain induces predominantly 1 form of leukemia, or in some cases various forms of leukemia can be induced by a single virus stock. It remains to be determined, however, whether the leukemogenic potential lies solely with the virus or whether the influence of the target cell may be equally important.

There are many theoretical considerations associated with prevention and control of leukemias in the animal systems, some of which have been voiced in the presentations in this Symposium. If one considers the immunological approaches that could be used for diagnosis, prophylaxis, and treatment of the disease, the leukemic cells or the infecting viruses are a ready source for some of the reagents necessary for such studies. In fact, diagnostic reagents for detection of virus, its genome, or expression of virus genetic information are well advanced and are utilized almost universally. These include the virus nucleic acids, the reverse transcriptase enzymes, and the structural proteins and glycoproteins. However, reagents specific for leukemic or preleukemic cells require further development.

Studies over the past several years have provided much insight into the nature of virion surface antigens as well as neoantigens expressed on the infected and transformed cell surface. In the avian system the major virion glycoprotein (gp85) is expressed on all virus-producing cells. Transformed cells contain, in addition, a new antigen termed TSSA, which is not a virion structural component (for details see Ref. 1).

In the murine system the major virion glycoprotein (gp71) is also expressed at the cell surface, but its presence is not necessarily coordinated with virus production (3, 6). Recent work, in fact, suggests that the expression of gp71 may be related to cellular transformation by the virus (3). There are several virus-induced cell surface antigens (some of which are probably other virus structural components), but as yet none have been found with well-defined transformation-specific properties such as avian TSSA (10). A very similar situation exists in the feline system with virion antigens and virion-induced cell surface antigens representing distinguishable entities on the cell membrane (5, 7, 12).

The strategic location of these antigens on the surface of leukemia cells clearly permits interaction with the host immune system. In fact antibodies to these components are present in the infected animals, and there are suggestions in some cases that the presence of sufficient antibody correlates in part with the absence of replicating virus and/or leukemia. There is obvious interest in obtaining purified components that are expressed on the cell surface for use in immunodiagnosis, immunoprophylaxis, or immunotherapy studies in animal leukemias. A brief summary of the work in 3 animal model systems pertaining to immunization with purified reagents indicates a great deal of promise and emphasizes the importance of continuing such studies.

Avian System

The virion glycoprotein (gp85) and the TSSA have both been purified to homogeneity by Bauer et al. (2). Chicken or rabbit antisera reacting with gp85 are cytotoxic for target cells expressing the antigen (2). Immunization of chickens with gp85 protected against challenge with infectious virus. Humoral antibodies and cytotoxic lymphocytes specific for TSSA and capable of in vitro lysis of cells transformed by avian agents could also be shown (2). Immunization studies with TSSA are in progress.

Murine System

Immunization of mice with gp71 purified from Friend murine leukemia virus was shown by Hunsman et al. (8) to be effective as a deterrent for Friend virus-induced leukemia. No replicating virus was found in the animals treated with the appropriate gp71 regimen. Analysis of the host immune response to determine which of the effector arms is of primary importance is in progress, and preliminary results indicate that T-cell recognition is part of the immune response (9). Attempts to immunize against other forms of leukemia including those that are spontaneous, induced by radiation, or induced by heterologous viruses will determine the broadness of the response (in progress). Immunotherapy with goat antiserum to gp71 1 week after virus challenge also prevented leukemia and eliminated the virus (8). Long-range immunotherapy studies including those in leukemic animals have been initiated.

Feline System

Purification of the analogous virion and cell surface antigens in this system is still in progress but surveys of the immune response to these components by several laboratories (5, 7, 12) suggest that use of purified antigens will also be effective. Preliminary studies (4) have shown that...
whole-virus vaccines induce levels of neutralizing antibodies in the cat that under natural conditions would be protective against virus infection and leukemia. In particular, because feline leukemia is a disease transmitted horizontally by the virus, developing subunit vaccines against the virus as a deterrent for leukemia is an obvious approach.

General Considerations

It would appear that the next several years will be most encouraging for further development of regimens to combat animal leukemia. The successful active immunization and passive immunotherapy trials against virus-induced leukemia in mice make it possible to carry out a detailed analysis of the mechanism of immunity induced by the viral glycoprotein. Because of the absence of genetic materials such as would be present in live or attenuated viral vaccines, or possible also in impure membrane extracts, these approaches would provide a more palatable model for similar attempts in human cancers. The applicability of studies in the animal model systems to human leukemia is underscored by several investigations that indicate the presence of oncornavirus footprints in human malignant cells. Recent work in our laboratories at Duke University suggests that some antigenic determinants of the viral gp71 glycoprotein and the major structural protein (p30) cross-react with surface antigen(s) and human myelogenous leukemia cells (11). That antisera to the virion components could be used as a diagnostic tool for certain kinds of human leukemias appears highly promising. Isolation and characterization of the related antigens on human leukemia cells is in progress and hopefully will provide more specific reagents that may prove useful in prevention and control of the disease in humans.

References

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