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DNA Sequence Analysis of a Stealth-Adapted Simian Cytomegalovirus

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Abstract

Stealth-adaptation is a mechanism that allows cytopathic viruses to evade immune elimination through the deletion of genes coding the major antigens targeted by the cellular immune system. A prototype stealth-adapted virus cultured from a patient with chronic fatigue syndrome (CFS) was readily transmissible to cats in which it induced an acute encephalopathy without localizing neurological signs. Vacuolating cellular damage was observed in many tissues of the animals, including the brain, in the absence of an accompanying inflammatory response. The cultured virus was cloned and partially sequenced. It comprises a fragmented, genetically unstable, genome. It has viral sequences that can be aligned to various regions of the genome of human cytomegalovirus (HCMV). Where the comparison can be made, the sequences match much more closely to those of African green monkey simian cytomegalovirus (SCMV), indicating an unequivocal origin from SCMV. In addition to SCMV-derived sequences, the cytopathic virus has acquired both cellular and bacteria-derived DNA. Cellular sequences include putative oncogenes and sequences related to those of endogenous retroviruses. Many of the bacterial sequences match closely to known genes of *Brucella*, while other genes show greater homology either to mycoplasma or

to Streptococcus. The presence of bacteria-derived sequences has led to the secondary designation of this type of novel microorganism as viteria. Molecularly heterogeneous viruses, inducing similar characteristic cytopathic effects in culture (and when examined, non-inflammatory vacuolating cellular damage in brain and other tissues), have been cultured from numerous patients with severe neurological, psychiatric, immunological and neoplastic diseases. The differing clinical manifestations in infected patients may reflect the assimilation of different cellular and other sequences in various stealth-adapted viruses. Tissue culture provides a valuable screening method for the detection of stealth-adapted viruses and for characterizing novel virus-associated products. Cultures can also help avoid the misidentification of stealth viruses for conventional viral and bacterial pathogens purportedly associated with chronic diseases.

Introduction

Chronic illnesses are typically categorized according to the predominating clinical manifestation. Accordingly, they come under the purview of different types of medical specialists, such as psychiatrists, neurologists, rheumatologists, endocrinologists, cardiologists, gastroenterologists, oncologists, etc. While this specialization fosters expertise in diagnosis and therapy, it tends to deemphasize the overlapping clinical features shared by many chronic debilitating illnesses. Symptoms such as fatigue, insomnia, impaired mood and cognition, widespread aches and pains, etc., typically occur in most chronically ill patients regardless of the underlying diagnosis. Individual patients will not uncommonly qualify for having two or more chronic diseases while family histories often reveal a constellation of medical problems among different family members. While most acute infections tend to give rise to a consistent clinical pattern of illness, this is not the general rule for chronic viral or bacterial infections. It is conceivable, therefore, that a common chronic infectious process could be involved in the currently widely recognized increases in many types of chronic illnesses. This consideration does not exclude important additive contributions of genetics, psychosocial, other environmental factors, autoimmunity, etc., in individual patients leading to their particular complex disease process. To help stem the ever increasing prevalence of chronic illnesses, it is vitally important not to overlook an infectious and, therefore, potentially contagious component. This paper reviews evidence that implicates chronic non-inflammatory, stealth-adapted viruses in many forms of human and animal diseases.

Stealth-adaptation refers to the ability of a conventional cytopathic (cell damaging) virus to lose portions of its viral genome that includes genes coding for components normally recognized by the cellular immune system. Although not widely appreciated among most virologists, only a relatively few number of virus coded

components provide the target antigens for the vast majority of anti-viral cytotoxic T lymphocytes (CTL). Deletion of these few select genes can essentially enable a virus to avoid effective immune recognition. The best studied stealth-adapted virus is a derivative of an African green monkey simian cytomegalovirus (SCMV). This virus presumably arose from an SCMV contaminated vaccine, such as a live polio virus vaccine. These vaccines were routinely produced in fresh kidney cell cultures obtained from African green monkeys. In a 1972 joint Lederle-Bureau of Biologics cooperative CMV study¹, all eleven monkeys studied demonstrated the presence of CMV-like agents. Seven of the monkeys would have passed [Lederle's] existing test standards; only one of these monkeys would have passed test methods using Lederle's 130 human diploid cell strain. Lederle proposed that it would begin treating monkeys with DNA antagonists during their isolation period, then remove the kidneys and test exhaustively for the presence of CMV in the kidney tissue. Even assuming that this was done, it is disturbing that 3 of 8 tested lots of live polio virus vaccine released later in the 1970's were recently confirmed as containing SCMV DNA². The present paper will provide a brief summary of studies leading to the isolation and subsequent molecular characterization of a stealth-adapted SCMV-derived virus.

Stealth Virus Detection and Isolation

The research program began in 1988 as a search for a viral cause of the chronic fatigue syndrome (CFS). It was based on the recent description of human herpesvirus-6 (HHV6), and on the availability of a highly sensitive molecular diagnostic assay, known as the polymerase chain reaction (PCR).³ The PCR assay comprises reacting a sample with relatively short pieces of synthesized DNA (primers) that selectively bind to the flanking sequences of a relatively small section of double

stranded DNA present in the particular sample being tested. The DNA is subjected to repeated rounds of heating to separate the DNA strands, cooling to allow the primers to bind and to be extended by DNA synthesis mediated by a heat resistant DNA polymerase enzyme. This process leads to exponential amplification of the targeted section of DNA, which greatly facilitates its detection and sequencing. Although PCR assays can be exquisitely sensitive, they can yield misleading information. For example, if a pathogen has a mutation or deletion in the targeted section of DNA, a negative PCR assay can result even though much of the remaining parts of the microorganism may be present. Conversely, if the primers are directed against sequences that are partially shared by different microorganisms, spurious identifications can be made based on a positive PCR. In spite of these limitations, PCR assays have proven extremely useful in the search for unexpected pathogens, including as detailed below the detection of stealth-adapted viruses.

The initial PCR assay employed was based on limited known DNA sequences of HHV6. The assay generally yielded negative results in patients with CFS. The PCR assay was modified so as to be cross-reactive with other known human herpesviruses. Other PCR primer sets were also designed to detect various retroviruses. The PCR assays were shown to be even broadly cross-reactive than anticipated, with for example, amplification occurring with adenoviruses by the herpesvirus-reactive primers. The assays were applied to blood samples of CFS patients. Depending on the conditions used, positive responses were seen with approximately a third to a half of the patients tested.³⁻⁵ Parallel testing of blood samples from the vast majority of apparently healthy individuals gave negative results. Some of the positive patient responses were quite striking in their intensity. The importance of the work became apparent when very strong PCR reactivity was seen using a cerebrospinal fluid (CSF) sample from both a newborn child with hepatosplenomegaly, seizures, and impaired

neurological development. This finding was followed shortly by a similar strong reactivity using CSF obtained from an adolescent with major neurological damage resulting from what had been considered a missed diagnosis of herpes simplex encephalitis. In both cases the CSF was totally devoid of any cellular inflammatory reaction and routine virus culture assays were reported as being negative. A positive PCR was also seen using a portion of a stereotactic brain biopsy performed on a school teacher with periventricular lesions identified using magnetic resonance imaging (MRI).⁴ Again, the striking feature of the brain biopsy was the lack of any inflammatory reaction. The brain cells did, however, show lipid filled vacuoles, damaged mitochondria and accumulations of irregularly shaped pigmented inclusions. These observations were consistent with non-inflammation-inducing cell damaging (cytopathic) viruses causing a spectrum of neurological illnesses. The term “stealth” was introduced to convey the apparent ability of the viruses to avoid effective immune recognition that would trigger an anti-viral inflammatory reaction. The task was to isolate such a “stealth-adapted” virus.

Many types of viruses can be detected by observing for a cytopathic effect (CPE) on cells grown in tissue culture. Using standard viral culture techniques suitable for the detection of human cytomegalovirus (HCMV), highly suggestive, but non-persisting cellular damage had previously been observed in cultures performed on numerous CFS patients. Clearly positive PCR assays were obtained on blood samples of a patient who experienced an encephalitis/meningitis-like illness in July 1991. A determined effort was made to culture her blood. After some 6 weeks delay, a strong sustainable cytopathic effect was observed.⁶ This individual has remained cognitively impaired with personality changes and marked fatigue. She has remained on disability with a diagnosis of CFS.

The striking tissue culture finding was the formation of foamy vacuolated cells that were comparable to what were seen in the brain biopsy. Repeated cultures from this patient provided similar positive results with the additional observation that the CPE would develop much earlier if the culture medium was frequently (daily or every 2nd day) replaced with fresh medium. The positive culture did not react in standard serological typing assays using antibodies specific for conventional human herpesviruses (CMV, HHV6, Varicella zoster, Herpes simplex or Epstein Barr), nor for enteroviruses or adenoviruses. It was also negative for human CMV and HHV-6 using specific PCR-based assays. The patient-derived cytopathic virus was successfully cultured in multiple cell lines from human and animal sources⁶ and could even replicate in insect-derived cells. Virus aliquots were submitted to the American Type Culture Collection (ATCC) for long term storage and public access (Accession number VR 2343).

Soon, thereafter, a slightly differing appearing, but otherwise very comparable, strongly positive culture was obtained in a physically different laboratory. The CPE developed in human fibroblasts three weeks after being inoculated with a CSF sample from a patient with a 4 year history of a bipolar, manic depressive illness. The woman had deteriorated clinically and developed seizures prior to admission to L.A. County Hospital. An aliquot of the second sample was sent to the Los Angeles County Public Health Laboratory. Following confirmatory culturing, the County laboratory reportedly sent a sample to the California State Laboratory. This virus was not identified by either the County or State laboratory and was dismissed as a probable contaminant. Electron microscopy on both of the patients' cultures confirmed the presence of numerous herpesvirus-like particles.

Many additional blood and occasional CSF samples were found to induce a foamy vacuolating CPE in viral cultures on both human fibroblasts and rhesus monkey

kidney cells. Adjustments to the culturing techniques, especially the use of serum free medium, frequent replacement of the medium, and freeze-thawing of the cells prior to culturing, led to the more rapid development and greater intensity of the CPE. The basic feature of positive cultures was the transformation of the normally thin, spindle-shaped fibroblasts into swollen, rounded, vacuolated, foamy (fat-filled) cells, with a tendency to form clusters. The extent of cell swelling, size of cell clusters, formation of syncytia from cells fusing with one another, amount of fat accumulation both in the cells and in the medium, and the extent and appearance of accompanying accumulations of fine to coarse pigments, all varied more or less independently between the cultures obtained from different individuals. Consistent positive/negative readings, as well as more detailed descriptions of the positive cultures were obtained by impartial observers and the distinction between patient and control populations confirmed in several double-blinded studies. The positive patients had a wide variety of neurological, neuropsychiatric and auto-immune diagnoses.⁷⁻¹⁰ Families were identified with various diagnoses among the different family members, but with very similar cytopathic changes seen in cultures.

Animal Studies

Cells from the virus culture of the initial culture positive CFS patient were inoculated into cats. The cats experienced profound behavioral changes.¹¹ Within a week they transformed from friendly, frisky happy-go-lucky favorites of the University animal facility, to frightened, reclusive animals shying away from the light. Several of the cats developed bald areas of skin upon their heads and necks from rubbing against the cage. Some had exudates from their nose from scratching. Gentle handling of the animals revealed painful muscles and enlarged lymph nodes. The acute illness peaked

at 1-2 weeks with significant clinical recovery seen in the animals maintained from 5-16 weeks post inoculation. Necropsy showed widespread non-inflammatory vacuolating cellular changes. Heat killed virus did not induce disease, and in fact, provided protection against subsequent inoculations of the same virus. The animal became ill when inoculated with a virus isolated from a different patient who had been diagnosed with systemic lupus erythematosus. Animals of patients were also reported to show various symptoms, and yielded positive cultures when blood samples were tested. Blood samples from ill cats were inoculated into healthy cats that subsequently became ill and virus culture positive.

Sequencing Studies

The primer sets that gave positive responses PCR reactions in the blood of the virus culture positive patient with CFS, also yielded strong reactions when tested on each of several repeat positive cultures from this patient. Two PCR products of approximately 1.5×10^3 nucleotides were isolated and sequenced.⁶ One product (GenBank accession number U09212) contained a sequence that showed a statistically significant homology to a region of the genome of HCMV corresponding to the UL34 gene (UL refers to the Unique Long segment of the human CMV genome. The genome also contains numbered genes from the Unique Short, US, segment, with both segments flanked by a series of repeated sequences). The other product (GenBank accession number U09213) did not match to the HCMV genome, or at the time to any other viral, cellular or bacterial sequence. A description of the initial culturing and growth characteristics of the virus, along with an analysis of the sequence data was published in 1994.⁶

DNA was isolated from the prototype culture using ultracentrifugation to isolate viral particles. In the first series of experiments, the DNA was cut with the enzyme EcoRI. In a second experiment agarose gel banded purified DNA was cut with the

enzyme *SacI*. The cut DNA was cloned into plasmids and many of the clones were sequenced. As each sequence became available for analysis, it was compared with the known complete sequence of HCMV, and the available sequence data of all other viruses, including CMV of various animals.

The sequence of some of the clones corresponded to regions for which the sequence data were available on both rhesus cytomegalovirus (RhCMV) and African green monkey simian cytomegalovirus (SCMV). Sequence comparison led to the unequivocal conclusion that the virus had originated from a SCMV.¹² By comparing PCR results using primers sets directed against sequences of other parts of the stealth virus and other regions of SCMV, it was clear that the stealth virus had diverged significantly from SCMV. It lacked several genes corresponding to known regions of HCMV that would also be expected in SCMV. An update of these data is that also includes comparison with baboon CMV (BaCMV) is provided in Table 1.

Much of the sequence data were included in a series of peer-reviewed publications,¹³⁻¹⁸ and submitted to GenBank. Most noteworthy were the findings indicating: i) Apparent lack of genes coding the virus components known to be targeted by the majority of cytotoxic T lymphocytes reactive with CMV infected cells. ii) Genetic instability and fragmentation of the virus genome. iii) Incorporation of cellular sequences, including a potential cancer causing gene, into the stealth virus. iv) Increased gene-copy number, when compared to HCMV, of the US28 gene. This gene codes a cell receptor molecule that binds to a class of cell activators, termed chemokines, which belong to a group of cell signaling molecules called cytokines. More interestingly, the US28 gene product provides a cell entry molecule for HIV. v) Presence of unusual bacteria-derived sequences in the culture. Several of the sequences matched very closely (but not identically) to alpha-proteobacteria, especially *Brucella*. The homology extended to the spirochete *Borellia* (the cause of

classic acute Lyme disease). Other sequences matched more closely to mycoplasma (implicated in CFS and Gulf war syndrome), Streptococcus (implicated in childhood obsessive compulsive disorders and PANDAS syndromes) and to other distinct types of bacteria. The finding of these sequences raised the distinct possibility that stealth virus infected patients could be mistakenly identified as being infected with these various types of bacteria. vi) The second PCR product isolated from the original stealth virus culture was shown to unequivocally correspond to the UL19 region of SCMV. vii) A closely related sequence was identified in a PCR product isolated from the patient with the bi-polar illness.¹⁹

Disease Outbreaks

The infectious nature of stealth-adapted viruses has been repeatedly suggested by individuals reporting their illness beginning shortly after a sexual and even non-sexual encounter with a symptomatic individual. Some patients have linked their illness to having received a blood transfusion or gamma globulin injection. Distinct community wide outbreaks have also come to the attention of various clinicians. One such outbreak occurred in the Mohave Valley region of Western Arizona in the spring of 1996.²⁰ Over 100 patients presented during a three month period with an acute gastrointestinal syndrome, followed by persisting fatigue, cognitive dysfunction and personality changes. Since then the community has experienced widespread chronic illnesses, including heightened allergies, chemical sensitivities especially to pesticides, higher than expected learning disorders among its children, and a high incidence of both depression and psychosis. Stealth virus cultures from these patients were consistently positive and distinguishable from control cultures in both routine and in double blinded independent studies. The clinician overseeing many of these cases

encountered at least 10 fatalities among symptomatic, virus-culture positive, middle-aged individuals. He also referred a child with a slowly evolving behavioral and learning disorder.²¹ An organic component was finally recognized by his parents, both of whom were physicians. In spite of an essentially normal clinical neurological examination, an MRI showed extensive sub-cortical T1 and T2 abnormalities. A brain biopsy showed the characteristic foamy vacuolating changes seen in other patients and in stealth virus inoculated cats. Mitochondria damage and intracellular inclusions were also evident. Both the mother and her son were culture positive. The child showed a significant response to ganciclovir (an anti-herpesvirus drug). The infecting virus could not be identified as a derivative of SCMV using a PCR based assay. This virus was also deposited with the American Type Culture Collection (Accession number VR-2568). Other community wide outbreaks of stealth-adapted viruses have been partially investigated and include Joelton, TN and Peoria, IL. As noted above, illnesses occurring within families also attest to the potential infectious nature of stealth-adapted viruses. Positive cultures and PCR based assays have also frequently been obtained from cancer patients including patients with salivary gland tumors,²² breast cancers and multiple myeloma.

Stealth Virus Inhibitor

Experience gained with the culturing of stealth-adapted viruses indicated the need to frequently replace the tissue culture medium. It was presumed that some factor or factors were accumulating in the cultures that were preventing the progression of the CPE. Insight into the inhibitory substances has come from recent studies on the aggregated pigmented intracellular materials seen in the virus cultures²³ and in the vacuolated cells present in various brain biopsies.²⁴ These materials are potentially providing an alternative energy source for the infected cells. The mineral

containing pigments appear capable of converting various forms of physical energies to chemical energy.²³ They have been designated alternative cellular energy pigments (ACE)-pigments.

Summary and Conclusions

The following conclusions can be drawn from the work. i) Atypically structured, non-inflammation inducing (stealth-adapted) cytopathic viruses definitely exist. ii) Some of these viruses were derived from SCMV and have presumably entered the human population from SCMV contaminated polio vaccines. iii) Stealth-adapted viruses can be regularly cultured from patients with complex multi-system illnesses, including various cancers. iv) Stealth-adaptation is considered to be a generic process that can involve many types of cytopathic viruses. It presumably occurs through the loss of genes coding for major antigens normally targeted by the cellular immune system. v) Tissue culture provides the best means to screen for stealth-adapted viruses. Viral cultures can also provide useful insights into pathology, including formation of lipids, and energy transducing pigments. vi) The production of lipids and pigmented material is viewed as a reparative process helping to maintain cell viability. This is based on the marked reduction in the intensity of the cytopathic effect if the culture medium is not frequently replaced. vii) Bacterial and cell derived genes are in the SCMV-derived stealth virus culture. This finding indicates the potential intermixing of cellular, viral and bacterial genes in the creation of new highly pathogenic microorganisms. viii) Stealth viruses are found in certain cancer patients, most of whom have symptoms of an underlying neuropsychiatric illness. The prospect of bacteria transmitting cancer causing viruses is a very serious and urgent public health concern. ix) Bacterial genes can help explain partial and inconsistent serological and PCR diagnostic findings for different bacteria in stealth virus infected individuals. x) The present studies provide support for an infectious process as a major contributing factor in the etiology of many chronic illnesses including cancer.

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Table 1. SCMV Related Genes in the Cultured Stealth-Adapted Virus

| CMV-Related | | Matching of Stealth Virus Sequences to | | | | |
|--------------|---------------|--|-----------|---------|-----------|---------|
| Contiguous | | SCMV | BaCMV | RhCMV | HCMV | |
| Sequences | | nucleotide matching (Expect value) | | | | |
| <u>Genes</u> | <u>Length</u> | | | | | |
| UL 14 | 1,458 | | | | | |
| UL 19-48 | 38,262 | | | | | |
| UL 48-54 | 8,407 | UL50 | 571/598 | 422/465 | 384/453 | 159/185 |
| UL 56 | 767 | | (0.0) | (e-180) | (e-95) | (e-38) |
| UL 57 + ori | 2,748 | UL57 | 1226/1246 | 499/577 | 1011/1265 | 370/492 |
| UL 61-69 | 4,459 | | (0.0) | (0.0) | (0.0) | (e-62) |
| UL 70 | 1,729 | | | | | |
| UL 71-76 | 6,328 | | | | | |
| UL 77-78 | 1,884 | | | | | |
| UL 84-104 | 25,023 | UL93 | 630/656 | 575/647 | 368/406 | 266/317 |
| UL 104-105 | 1,464 | | (0.0) | (0.0) | (e-137) | (e-57) |
| UL 111-112 | 1,955 | UL111 | 760/807 | 709/901 | 74/89 | 75/89 |
| UL 115-132 | 8,628 | | (0.0) | (e-171) | (e-7) | (e-15) |
| UL 141-144 | 5,820 | | | | | |
| US18 | | | | | | |
| US 20-29* | 16,011 | | | | | |
| US 30-32 | 3,978 | | | | | |

Analysis based on >300 clones of DNA of stealth virus culture. There is good evidence that the virus has a fragmented, unstable genome. Note apparent absence of UL 83 and UL 55. The UL 123 showed significant mutations. The products of these three genes would ordinarily provide the major antigens recognized by anti-CMV cytotoxic T cells. The nucleotide homology data establish that this particular stealth-adapted virus was derived from SCMV.

* 5 copies of US28 related gene: a chemokine (and also HIV) receptor.