Human and Nonhuman Primate Lentiviral Infection and Autoimmunity

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ABSTRACT: The goal of this communication is to summarize the following—the types of autoimmune responses that have been characterized in human HIV-1 infection; the potential mechanisms that were initially thought to be the basis for such autoimmune responses; the prevalence and incidence of conventional autoimmune diseases with HIV-1 infection; the spectrum of autoimmune disorders following the institution of HAART and its associated mechanisms; the role of such autoimmunity in SIV-infected nonhuman primates; and the molecular basis for autoimmune responses, such as the role of exosomes in lentiviral disease.

KEYWORDS: HIV-1; SIV; human; nonhuman; primates; autoimmune; infection; lentivirus

INTRODUCTION

The consequences of lentiviral infections, such as HIV-1 in humans and SIV in Asian rhesus or pig-tailed macaques, are remarkably similar.\textsuperscript{1} Both of these lentiviruses cause an AIDS-like disease exemplified by depletion of CD4\textsuperscript{+} T cells, a gradual loss of memory T cell response, a state of immunodeficiency, increased susceptibility to opportunistic infections, diarrhea, weight loss, and ultimately death. Ever since the discovery of the etiology of AIDS, there have been several studies that have documented the occurrence of autoantibodies against a number of self-antigens,\textsuperscript{2–5} the presence of cytotoxic T cells\textsuperscript{6–8} with specificity for autologous non-infected CD4\textsuperscript{+} T cells (believed to contribute to CD4\textsuperscript{+} T cell loss), and the association of HIV-1 infection with a number of autoimmune diseases, such as rheumatoid arthritis, SLE, etc.\textsuperscript{9} Induction of such immune responses in the setting of immunodeficiency was considered somewhat of a paradox because such patients have been noted to gradually lose antigen-specific memory T cell responses and demonstrate reduced responses to primary immunization with conventional vaccines that correlated with CD4 counts and viral loads. These associations of HIV-1 infection with

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doi: 10.1196/annals.1313.091
autoimmune diseases, often with contradictory interpretations, were considered complex because of a variety of findings; an example is listed here to provide one explanation for the loss of interest in defining relationships between HIV infection and autoimmune disease. Thus, it was noted that patients with rheumatoid arthritis (RA) demonstrate activated CD4+ T cell and macrophage/dendritic lineage cells in the synovium during acute disease flare-ups. These are the precise lineages that are the target of HIV infection and, as such, they become an excellent target for HIV infection with several consequences. First of all, they would serve to increase viral loads and, second, the local inflammatory responses against HIV would be additive to the autoimmune-mediated inflammatory response, making the disease worse. Antiviral therapy for such patients has in select cases shown to lead to not only a decrease in viral load, but also to lead to remission from their autoimmune rheumatoid disease. However, the introduction of highly active antiretroviral therapy (HAART) has in these cases of RA exacerbated the rheumatoid disease. Interest in the role of autoimmunity in the pathogenesis of HIV-1 and SIV-induced disease in human and nonhuman primates thus waned, until recently, not only because of the discovery of such complexities in clinical presentations, but also because of the more urgent need to define antiviral chemotherapies and to develop effective vaccines.

Two issues have brought back a renewed interest in the role of autoimmunity in HIV disease. Thus, first a relatively longer follow-up study of patients placed on HAART led to the discovery that such therapy leads to a disease termed “immune reconstitution syndrome”, which has clinical features typical of autoimmune diseases. This syndrome has also been termed “immune restoration disease” and “immune restoration inflammatory syndrome” (IRIS), all of which are basically the same clinical disease reflecting different scales of disorders of the immune system. Second, an increased understanding of the molecular basis by which lentiviruses are packaged has led to the discovery of a role for “exosomes”, which could potentially play an ever-increasing role not only in the pathogenesis of HIV, but in the induction of autoimmune disease. These two issues are discussed below in some detail. Thus, the goal of this communication is to summarize the following: our knowledge of the types of autoimmune responses that have been characterized in human HIV-1 infection; the potential mechanisms that were initially thought to be the basis for such autoimmune responses; the prevalence and incidence of conventional autoimmune disease with HIV-1 infection; the spectrum of autoimmune disorders following the institution of HAART and its associated mechanisms; the role of such autoimmunity in SIV-infected nonhuman primates; and, last, our current understanding of the molecular basis for autoimmune responses, such as the role of exosomes in lentiviral disease.

TARGETS OF AUTOIMMUNE RESPONSES

Basically, autoantibodies that have been identified in the sera of HIV-1-infected patients can be divided into three distinct but overlapping groups of autoantigens. These include autoantibodies against cell surface molecules such as CD4, MHC class I and II, TCR, and Fas, to name a few, organ-specific autoantibodies such as antiplatelet antibodies, anti-cardiac myosin antibodies, anti-smooth muscle-specific antibodies, and anti-erythroid cell-specific antibodies, and, lastly,
nonorgan-specific antibodies such as antinuclear antibodies, antihistone antibodies, anti–double-stranded DNA antibodies,\textsuperscript{21–24} and antiphospholipid antibodies.\textsuperscript{25} Each of these categories of antibodies has been characterized to contribute to the pathogenesis of human HIV-1 infection. Thus, autoantibodies against cell surface molecules have been reasoned to lead to depletion of CD4\textsuperscript{+} T cells\textsuperscript{26} by either complement-mediated activation or antibody-dependent cellular cytotoxicity-mediated effector mechanisms.\textsuperscript{27,28} Autoantibodies against platelets and cardiac tissue myosin have been thought to contribute to thrombocytopenic purpura and myocarditis. Other autoantibodies have been thought to contribute to systemic autoimmune disease. Some of the issues that remain unresolved in reviewing the results of all these studies is whether the extent and severity of autoimmune disease is worse if the autoimmune disease precedes HIV infection and whether the autoimmune disease that is seen in HIV-infected patients is due to an existing predilection to develop autoimmune disease and was not induced by HIV infection, and thus was a comorbid condition. These issues are difficult to address objectively because most autoimmune diseases are manifest at later stages of life than cohorts that acquire HIV infection, and the number of cases that can be studied to address such issues at any given single clinical center appear limited.

POTENTIAL MECHANISMS IMPLICATED IN THE AUTOIMMUNITY OF HIV-1-INFECTED PATIENTS

To a large extent, the mechanisms which investigators outlined as the basis for the occurrence of autoimmune disease in HIV-infected patients were no different than those discussed for standard autoimmune diseases. Thus, one of the major hypotheses put forward was that of a role for molecular mimicry in the induction of autoimmune antibodies in the plasma of HIV-1-infected patients. Hence, similarity between a number of HIV proteins and self-molecules was identified.\textsuperscript{28,29} This included the finding of the reactivity of anti-gp41 antibody against human MHC molecules.\textsuperscript{28} Detailed structural and sequence analysis of the HIV-1 gp-41/gp120 led to the concept of a high degree of homology between self-molecules and HIV-1.\textsuperscript{30,31} These findings were followed by the reports of the occurrence of anti-idiotypic antibodies against gp-120 and the role such anti-idiotypic antibodies may play in the induction of autoimmune responses secondary to binding of such antibodies to the CD4 molecule. Thus, the view that was put forward was that “molecular complementarity” exists between the binding sequence of HIV-1 gp120 and the CD4 molecule and that anti-idiotypic antibodies against gp120 would have the potential of binding to the CD4 molecule and lead either directly or indirectly to the elimination of the CD4\textsuperscript{+} T cells and/or dysregulate the induction of immune responses, contributing to the generation of autoimmune disease.\textsuperscript{32} A third mechanism that received considerable attention concerned the potential ability of select HIV-1-encoded proteins to serve as “superantigens”. The HIV-1-encoded proteins included gp120\textsuperscript{33} and HIV-1 “nef”.\textsuperscript{34} While the mechanisms by which HIV gp120 serves as a superantigen have been defined primarily in terms of the ability of the gp120 molecule to bind selectively to the VH3 Ig gene-encoding family and to B cells that express VH3 Ig,\textsuperscript{35} the ability of the HIV-1-encoded “nef” gene has been somewhat controversial.\textsuperscript{36} Some studies have also documented polyclonal B cell activation as a consequence of HIV-1 infec-
tion and have reasoned this activity to lead to hypergammaglobulinemia, which has been well characterized in HIV-1-infected individuals. More recently, a role for regulatory T cells (Tregs) has been implicated in HIV-1-infected patients. This issue is important because a major role of a dysregulation of this cell subset has been implicated in a variety of autoimmune diseases; such cells are known to maintain tolerance to self-antigens and control autoimmunity. Thus, it has been shown in one study that removal of CD4+ CD25hi–expressing cells from the PBMCs of HIV-1-infected patients resulted in enhanced HIV- and CMV-specific immune response. In addition, in a separate study, it was shown that the presence of a significant frequency of such Tregs was beneficial to HIV-1-infected patients because they suppressed and thus regulated T cell activation, proliferation, and cytokine synthesis, and their presence was correlated with decreased viral load. Thus, while such cells may suppress virus-specific immune responses, they also suppress cell activation, thereby leading to less viral replication and lower viral loads. The precise role of such Tregs in regulating autoimmunity in HIV-1-infected individuals can only be hypothesized at this point because detailed studies of this subset in HIV-infected individuals with autoimmune disease—in particular, in the era of HAART—remain to be performed.

**HIV INFECTION AND THE INCIDENCE OF AUTOIMMUNE DISEASE**

As stated above, a plethora of autoantibodies has been catalogued from the sera from HIV-1 infected patients. These include antibodies against cardiolipin, DNA, small nucleoriboproteins (snRNPs), thyroglobulin, thyroid peroxidase, myosin, erythropoietin, to name a few. Similarly, a number of autoimmune diseases have been documented in HIV-1-infected patients. These include systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), vasculitis, PBC, antiphospholipids syndrome, polymyositis, Graves’ disease, ITP, etc. Early on, it was reasoned that loss of immunocompetence in HIV-infected individuals would make them more susceptible to opportunistic infections that could, in turn, lead to either the induction or exacerbation of an underlying autoimmune disease due to the likelihood of molecular mimicry. While most of the above data are derived from either single case reports and a limited number of prevalence studies, for example, the studies that document the prevalence of cryoglobulinemia and serological markers of autoimmune disease in 97 HIV-1-infected patients and the study of autoimmune hemolytic anemia associated with HIV-1 infection, there have been limited studies in the past on the true incidence of autoimmune diseases in HIV-1-infected patients. The reasons for this are not clear, but are likely due to the difficulty in the proper diagnosis of autoimmune disease in HIV-1-infected patients, or that autoimmune diseases and HIV target different populations, or that the immunological disorders are skewed and polarized such that they result in excluding each other. The prevalence/incidence is therefore too low and would require extensive and costly epidemiologic studies. Clearly, the epidemiological data appear to support this latter view. Thus, based on the available data and mathematical calculations performed in 1993, if there were 500,000 SLE patients and 220,000 AIDS patients in the United States, there would at least be 400 concurrent cases of HIV and SLE. This is clearly not the case because only 6 cases were reported in the period that this study was performed. Other
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reports similarly confirmed the low occurrence of SLE in HIV-infected patients\(^45\) and that chemotherapy in fact led to reactivation of SLE in the few patients who were co-infected.\(^46\) However, as stated above, now that we have had sufficient time to follow HIV-1-infected patients following the advent of HAART and have noticed the emergence of autoimmune disease in these patients,\(^47\) it is becoming increasingly clear that the reconstitution of the immune system in such patients is not optimal and has given rise to the introduction of a new lexicon in medicine termed “immune reconstitution disease”.

**IMMUNE RESTORATION DISEASE (IRD) OR IMMUNE RESTORATION INFLAMMATORY SYNDROME (IRIS)**

The fact that HAART-based therapy led to a marked decrease in the incidence of opportunistic infections (O.I.’s) and the resolution of O.I.’s in HIV-1-infected patients following HAART provided strong evidence that such chemotherapeutic strategies were effective in restoring immune responses in such patients.\(^48\) This view was further supported by the findings of increased CMV-specific cellular responses in HIV-1-infected patients co-infected with CMV accompanied by the lowering of CMV viremia.\(^49\) However, soon thereafter, a number of reports emerged on a series of “atypical” infections in patients following placement on HAART-based therapies that were considered inflammatory disorders in response to O.I.’s and thought to be initially due to partial and incomplete immune reconstitution.\(^50\) Since then, there has been a growing acceptance that a distinct clinical syndrome exists which appears to accompany patients that are placed on HAART who respond to such therapy by lowering of viral loads and regaining immune competence. The response of such patients to the pathogen in question is of pathogenic consequence and in select cases leads to death and can be viewed as an uncontrolled immune response against the pathogen. The syndrome has been given different names by different investigators, and until the pathogenic mechanisms are fully defined this problem will likely continue. It is also clear that learning the mechanisms by which such an overzealous immune response is initiated may lead to refined methodologies for the therapy and management of such patients. French *et al.*\(^51\) have divided the clinical immune restoration disease syndromes into three different types. One type includes syndromes with an infectious etiology and thus it is termed infectious IRD; a second type includes those with a granulomatous inflammation of the lungs and is termed sarcoid IRD; and the last category includes syndromes in which a new autoimmune disease occurs and/or an existing autoimmune disease is exacerbated, shortly after HAART-based therapies; it has been termed autoimmune IRD. Under infectious IRD, a description of mycobacterial infections is included, such as *Mycobacterium avium* complex, *Mycobacterium tuberculosis*, and *M. leprae,*\(^52\) cryptococcal infections, pneumocystis, hepatitis B and C infections, CMV, varicella zoster, herpes simplex, JC viral infections, and a few others (reviewed in French *et al.*\(^51\)). Under sarcoid IRD, the disease is distinct from typical HIV-associated sarcoidosis because it involves CD4\(^+\) T cells instead of CD8\(^+\) T cells and could be secondary to treatment with IL-2 as an adjunct therapy. The most common diseases included among the autoimmune IRD are SLE, polymyositis, and RA, followed by Guillain-Barré and Graves’ disease. Of interest has been the finding of reactivity against the CD4
molecule in HIV-1-infected patients on HAART.53 These patients have been a subject of a T cell vaccination protocol with the rationale that incomplete CD4+ T cell recovery in these patients was secondary to immune response against the CD4 molecule and that immunizing them with glutaraldehyde-treated enriched populations of their own anti-CD4 reactive cells (auto–anti-idiotypic therapy protocol) would be beneficial. Also of interest was the finding that such immunizations led to a decrease in anti-CD4 immunity in 5 of 7 patients with no effect on viral load.53 These are novel approaches that require additional studies to precisely assess the usefulness of such an approach. In general, it appears that infectious disease etiology–based IRDs occur relatively early following the institution of HAART, whereas noninfectious disease–based etiologies of IRD occur relatively late post-institution of HAART, although this may be an overgeneralization. It is also clear that therapeutic management of such patients is going to be rather complex. Thus, it will depend on the reason for the occurrence of the IRD, of which there may be many. Secondly, it could be due to incomplete immune reconstitution (holes in the immunological repertoire), contribution of genetic traits, selective loss of synthesis and/or response of a select number of cytokines such as Th1 versus Th2, a role for dysfunctional regulatory T cells, abnormal synthesis and/or response to growth factors, or a combination of these. Thus, additional studies are required to gain a better understanding of the mechanisms of these diseases before therapeutic strategies can be devised.

ROLE OF AUTOIMMUNITY IN SIV-INFECTED NONHUMAN PRIMATES

To date, there have been very few studies performed on characterizing the prevalence of autoimmune disease in SIV-infected nonhuman primates. There are several reasons. First, the focus on the use of SIV-infected nonhuman primates has been to utilize them to study candidate vaccines and antiretroviral drugs; this is appropriate because of the clinical need and importance of such studies. Second, the viral isolates that are being utilized are those that cause rapid disease so that answers to the efficacy of antiretroviral drugs and vaccines can be acquired in a timely fashion. Thus, the time course of experimental SIV infection and disease is relatively rapid compared with HIV-infected humans. It is unlikely that the disease pathogenesis secondary to autoimmune disease would be readily apparent in such a short time frame. In this context, it is important to note that whereas pathology directly related to autoimmune disease has been rarely reported, there clearly have been reports of the occurrence of autoimmune antibodies in SIV-infected nonhuman primates. These reports include the finding of autoimmune antibodies against histone H2B only in the sera of SIV-infected rhesus macaques, but not uninfected macaques.54 Of importance was the finding that such antibodies were not found in the sera of SIV-infected sooty mangabeys. This issue is discussed below. Other autoimmune manifestations that have been reported include the finding of autoimmune hemolytic anemia in SIV-infected rhesus macaques, which was determined to be multifactorial.55,56 There have also been reports of increased prevalence of cardiac disease in SIV-infected rhesus macaques.57 However, it is not clear whether this disease is secondary to autoimmune responses against cardiac tissue, due to myocyte loss secondary to innocent bystander effects or due to increased susceptibility to cardiotropic viruses that initiate the disease, which leads to myocarditis and later to cardiomyopathy.
An issue that has not been recognized widely in the HIV/AIDS research community is the complete lack of any signs of autoimmune disease in select African species of nonhuman primates including the species studied by our lab for the last two decades. Thus, sooty mangabey monkeys bred in captivity at the Yerkes Primate Center of Emory University are naturally infected with SIV, but to date have never shown any signs of SIV-associated clinical disease or of any autoimmune disease.\textsuperscript{58,59} This is not due to viral loads, route of infection, or lack of SIV-specific humoral immune response. Thus, some mangabeyes have had viral loads of >1 million viral copies/mL of plasma for years and have yet to show any signs of clinical disease. Clearly, such viral loads lead to disease and death of Asian macaques infected with SIV. Groups of SIV-seronegative mangabeyes have been experimentally infected intravenously with SIVmac239, but again, while they do get infected and develop viral and cellular viral loads and anti-SIV–specific antibody responses similar to SIVmac239-infected rhesus macaques, they have not shown any signs of clinical disease to date. Thus, there is a paradox within this species. If the SIV-specific immune response is protective of disease, then why do they continue to have high viral loads? If they have high viral loads, then why do they not develop disease? In the context of this review, why do these animals not develop any clinical signs of autoimmune disease if chronic infection is reasoned to be required to lead to autoimmune disease in HIV-1-infected humans? Thus, these issues need to be addressed. It is important to point out in this regard that our laboratory has screened sera from SIV-infected rhesus macaques and sooty mangabeyes. Only the sera from SIV-infected rhesus macaques appear to contain antibodies either against the cell line in which the virus is prepared (if a cell line is used for the preparation of the viral stock) or against rhesus PBMCs if day 3 PHA blasts from rhesus macaques are used to grow the viral stocks. The potential of such antibodies to induce pathology \textit{in vivo} has not been defined, and therefore the significance of such antibodies is not clear at present. Preliminary studies appear to suggest that such antibodies are primarily directed at MHC class I and II molecules and against costimulatory molecules such as CD80 and CD86. Such antibodies may contribute to immune suppression characteristic of such SIV-infected rhesus macaques.

\textbf{MOLECULAR BASIS FOR THE AUTOIMMUNE RESPONSE: THE EXOSOME HYPOTHESIS}

It is becoming increasingly clear that host proteins are in fact a significant component of lentiviruses as they emerge from infected cells. In addition, these virus particles either bud from the cell surface or exit from the cell in the form of multivesicular bodies (MVB) depending on the cell lineage in which they replicate (see Fig. 1). Thus, while these virus particles normally bud from the cell surface of both CD4\textsuperscript{+} T cells and macrophages, they form MVB when they are packaged within the macrophage lineage of cells.\textsuperscript{12} These MVB have been termed “exosomes” and are reasoned to be the “Trojan horses” for the infectious cycle in HIV infection.\textsuperscript{60} Exosomes like microparticles have also been shown to carry with them chemokine receptor molecules such as CXCR4, which are critical for entry of X4 tropic viruses into the appropriate target cells.\textsuperscript{61} Thus, coculture of such CXCR4 containing microparticles has been shown to transfer such chemokine receptors to cell lineages.
FIGURE 1. Steps in the infection, replication, and production of HIV-1 particles in (A) CD4+ T cells and (B) macrophages. The viral life cycle basically has four steps: entry; reverse transcription (RT) and integration into the host cell genome; viral transcription; and finally viral assembly and egress from the host cell. The figures are meant to signify differences in the assembly of the virus within CD4+ T cells and macrophages. Thus, as seen in the figure, virus predominantly exits from the CD4+ T cells via budding, but incorporates within it a number of host cell membrane proteins. In the case of macrophages, the virus can not only exit via budding, but also can form multivesicular bodies (MVB), which have also been termed “exosomes”. In this case, the virus also incorporates a variety of host cell proteins. Such host cell proteins carrying exosomes are hypothesized to play a role in the induction of immune responses against self-proteins.
that do not otherwise express such chemokine receptors and, importantly, such receptors are then decorated on the otherwise infection-resistant cell in a form that makes these cells now susceptible to HIV-1 infection. What is relevant for this review is that when such viruses replicate and emerge from these lineages they incorporate and carry with them a variety of host proteins. Of great interest is that the type of host proteins incorporated includes those that are involved in normal immune responses such as MHC class I/class II molecules, costimulatory molecules, etc., as well as molecules that are part of “lipid rafts” and constituents of the “immunological synapse”. These packaged virions are by themselves capable of inducing novel immune responses because the host cell MHC molecules that are part of the virions bear peptides that are likely also to be part of host cellular proteins, and in the presence of costimulatory molecules they maintain the potential to induce immune responses. There have been a few studies that have used exosomes as immunogens and have successfully utilized them as therapeutic vehicles for cancer.\textsuperscript{62,63} They have been found to be highly potent, inducing immune responses in the pg range.\textsuperscript{64} It has been suggested that this increased efficiency is due to the molecular nature of the assembly of the MHC and costimulatory molecules encompassing the virions. Also of great interest is that there are marked differences in the type of host proteins that get incorporated into such virions depending on the cell lineage in which they replicate. These findings have prompted a re-examination of the quality and specificity of the host immune response against lentiviruses by those involved in defining the role of host proteins in the immune response against lentiviruses. Our laboratory has become involved in the comparative analysis of the nature of the host proteins that get incorporated in virions emerging from CD4\textsuperscript{+} T cells and macrophage lineages both from SIV-infected disease-resistant sooty mangabeys that do not demonstrate any autoimmune responses and from SIV-infected disease-susceptible rhesus macaques that do develop autoimmune responses. The rationale is that the findings from such a study will help define the potential reasons for the difference in the ability to induce autoimmune responses and, more importantly, the distinct clinical outcome in these two species. Also, germane to this review, it may provide us with some clues as to the mechanisms of induction of autoantibodies in SIV-infected macaques, but not SIV-infected mangabeys. Preliminary data from such electrospray mass spectrometric analysis (extracts analyzed by ESI-MS, positive mode) already have shown differences in the types of proteins that are incorporated in SIV replicating within cells from macaques and mangabeys. Thus, whereas virions from CD4\textsuperscript{+} T cells from rhesus macaques appear to contain predominantly host cell cytoskeleton proteins, they also contain CD80 and a number of additional costimulatory molecules. SIV preparations from mangabeys on the other hand also contain cytoskeleton proteins; however, these are different from those from macaques and, in addition, contain proteins that are unique from proteins found in SIV preparations of macaque CD4\textsuperscript{+} T cells, but that have still to be identified.

CONCLUSIONS

The importance of a role for autoimmunity in the pathogenesis of lentiviral infection has had an undulating history. While autoimmune antibodies were recognized to exist in the sera of patients with HIV-1 infection and in SIV-infected non-
human primates, their importance in contributing to the pathogenesis of lentiviral infection and vice versa was not clearly defined. There were also reports that HIV-1 infection induced immunosuppression that in fact led to remission of a number of autoimmune diseases. While limited formal prevalence and/or incidence studies on the occurrence of autoimmune diseases in HIV-1-infected patients were conducted, it was generally considered that such occurrences were rare, most likely because the two diseases occurred in different population groups. More recently, however, two issues have once again rekindled the interest for the role of autoimmune disease in lentiviral infections. This includes the finding of the phenomenon of “immune restoration disease” and the more detailed understanding of the molecular mechanisms by which lentiviruses are assembled, packaged, and exit from the cells in which they replicate; this gives rise to the concept that these virions, especially in the form of exosomes, may play an important role in the immune response not only against the viral proteins, but also against self-proteins that become incorporated within the virions. Findings on these two issues contribute to our current concept of HIV pathogenesis.

ACKNOWLEDGMENTS

This work was supported by a grant from the National Institutes of Health (No. NIH-AI-27057).
N. Onlamoon is on leave from Mahidol University.

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