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REVIEW ARTICLE

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Role of HTLV-I infection in the pathogenesis of Sjögren's syndrome and rheumatoid arthritis

Abstract HTLV-I has been identified as a causative agent which initiates and/or perpetuates the process of Sjögren's syndrome (SS) and rheumatoid arthritis (RA). A high seroprevalence of HTLV-I infection has been determined in both SS and RA patients in the HTLV-I-endemic area of Nagasaki, Japan. HTLV-I proviral DNA and HTLV-I Tax/Rex mRNA are expressed in the salivary glands or synovial cells of HTLV-I-seropositive SS or RA patients, indicating that HTLV-I is present in the affected organs and modulates the process of the disease. Cellular functions are modulated by HTLV-I infection, showing that cell proliferation and cytokine production are upregulated in HTLV-I-infected cells, and this is in part mediated by the HTLV-I Tax-induced NF-κB activation of host cells. Furthermore, Tax-mediated NF-κB activation involves resistance toward apoptotic stimuli in HTLV-I infected cells. These modulatory effects of HTLV-I Tax are believed to be important in promoting autoimmune disorders such as SS and RA in HTLV-I-seropositive subjects.

Key words HTLV-I · NF-κB · Rheumatoid arthritis · Sjögren's syndrome · Tax

Introduction

The importance of viral infections in promoting the onset of human autoimmune diseases has been known for many years. Cellular functions have been shown to be modulated by viral infections, and both viral DNAs/mRNAs and viral proteins are detected in the affected tissues of human autoimmune diseases, including the synovial tissues of rheumatoid arthritis (RA) patients and the salivary glands of Sjögren's syndrome (SS) patients. One of the candidate viruses is the human T lymphotropic virus type I (HTLV-I).

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In this paper, we consider the close relationship between HTLV-I infection and Sjögren's syndrome (SS)/rheumatoid arthritis (RA) based on epidemiological, clinical, and experimental results.

High seroprevalence of HTLV-I infection in patients with SS and RA in the HTLV-I-endemic area of Nagasaki, Japan

HTLV-I is a human retrovirus originally identified as the etiological agent of adult T cell leukemia/lymphoma (ATLL),[1,2] and it is also closely associated with a slowly progressive myelopathy known as HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP).[3,4] We have examined the HTLV-I seroprevalence of female patients with SS and RA.[5–7] The seroprevalence of HTLV-I infection in females was 3.4% in normal blood donors in Nagasaki. In contrast, the HTLV-I seroprevalence in female SS patients was 23.0%, which was significantly higher than that of normal blood donors. The age-adjusted summary odds ratio of HTLV-I infection in SS patients, estimated by the Mantel–Haenszel procedure, was 3.1 as compared with normal blood donors. Furthermore, the etiological fraction, the proportion of SS patients attributable to HTLV-I infection, was estimated to be 17.6%. In addition to SS, the HTLV-I seroprevalence in RA patients was 20.4%, which was also significantly higher than that in normal blood donors. The age-adjusted summary odds ratio of HTLV-I infection in RA patients was 2.8, and the etiological fraction was estimated to be 13.2%. These findings suggest that the high seroprevalence of HTLV-I infection among SS and RA patients is not a simple coincidence in the endemic area, and that HTLV-I infection really is a risk factor for SS and RA.

Clinical features of HTLV-I-seropositive SS and RA patients

The occurrence of extraglandular manifestations such as uvetis, myopathy, and recurrent fever was higher in HTLV-

I-seropositive SS patients than in HTLV-I-seronegative SS patients.[5] The spontaneous proliferative response of peripheral blood (PB) mononuclear cells and the percentage of PB activated T cells (T cells expressing CD45RO, HLA-DR antigen, and CD25) were also higher in HTLV-I-seropositive SS patients than in HTLV-I-seronegative SS patients.[5] The serological characteristics of HTLV-I-seropositive and HTLV-I-seronegative SS have been examined. There was no significant difference between the two groups regarding serum concentrations of γ-globulin and IgG, and the prevalence of rheumatoid factor, antinuclear antibody, and anti-SS-A (Ro)/anti-SS-B (Ra) antibodies.[5] Salivary IgG- and IgA-class antibodies to HTLV-I were also examined in both SS patient groups, demonstrating that IgA class but not IgG class anti-HTLV-I antibodies were commonly determined in HTLV-I-seropositive SS patients.[6] These data indicate the presence of active immune responses to HTLV-I in the salivary glands of patients with HTLV-I-seropositive SS. A close association between HTLV-I infection and SS has also been proved by the fact that about 60%–70% of HAM patients also had with SS.[8,9] Interestingly, mononuclear cell infiltration was found in all the HAM patients when a biopsy of the labial salivary glands was examined.[8,9] Although we did not find any difference in the phenotypic characteristics of lymphocytes infiltrating into the labial salivary glands in HTLV-I-seropositive and HTLV-I-seronegative SS patients, the density of mononuclear cell infiltration was more prominent in HTLV-I-seropositive SS patients than in HTLV-I-seronegative SS patients.[9] The increment of co-stimulating molecule expression on PB lymphocytes[10] and that of transmigratory activity of PB $CD4^+$ T cells through reconstituted basement membrane in HAM patients[11] appear to be associated with the histopathological features of HTLV-I-seropositive SS patients. We have also shown that the quantity of HTLV-I proviral load in $CD4^+$ T cells of HTLV-I-seropositive SS patients appears to be important in the transmigratory activity of $CD4^+$ T cells.[11]

The presence of HTLV-I proviral DNA or HTLV-I tax/rex mRNA expression has been found in synovial cells and synovial fluid T cells in HTLV-I-seropositive RA patients,[12] suggesting that HTLV-I infection promotes the inflammatory process of rheumatoid synovitis. We tried to define the characteristics of HTLV-I-seropositive RA patients, but there were no significant differences in laboratory and clinical features between HTLV-I-seropositive and HTLV-I-seronegative RA patients, including the prevalence of rheumatoid factor, the clinical stages and functional classes, and the size of affected joints.[7]

Modulation of cellular functions by HTLV-I infection

Infection of human host cells with HTLV-I results in the activation of these cells and the induction of various cellular events such as increased production of various types of cytokines and augmentation of cell proliferation.[13–15] Isolated human synovial cells and endothelial cells can be target cells for HTLV-I infection, demonstrating that HTLV-I gene products were detected in both synovial cells and endothelial cells after co-cultivation with HTLV-I-infected cell lines.[16,17] The proliferative response of synovial cells and the cytokine production of both synovial cells and endothelial cells were upregulated by HTLV-I infection.[16,17] These events are believed to be initiated by transactivation of expression of host genes through the HTLV-I Tax protein.[18] The factor in host cells which induces gene expression by Tax is thought to be a set of enhancer-binding proteins.[18] One such factor is NF-κB, which is activated by Tax protein, and implicated in Tax-mediated transactivation of various genes. The use of the deletion constructs of the enhancer/promotor region of the IL-6 gene showed that NF-κB is an indispensable nuclear factor in stimulating the gene expression of IL-6 in HTLV-I tax transfectants.[19] Therefore, the increment of cytokine production and/or cell proliferation in synovial and endothelial cells induced by HTLV-I infection are suggested, in part, to be mediated by Tax protein.

Inflammatory reactions are supposed to be augmented by HTLV-I infection by NF-κB, and in addition, a newly described function of NF-κB is its inhibitory action toward apoptotic signals.[20–22] We tried to check the possibility that NF-κB is highly activated by Tax, and thus, HTLV-I-infected cells become resistant to apoptotic stimuli, resulting in increased production of cytokines and cell proliferation. The apoptotic process involves complex machinery regulated by the molecular interactions of various gene products.[23–26] One of the major gene products that induces apoptosis is the caspase family, which is conserved from nematodes to mammals.[23–26] Cells treated with NF-κB inhibitors rapidly underwent apoptosis, which was associated with the activation of caspase-8 and caspase-3. In contrast, the activation of caspase-8 and caspase-3, as well as the apoptotic cell death induced by NF-κB inhibitors, were markedly inhibited by the introduction of Tax protein.[27] Two major protein families, Bcl-2-related proteins and the inhibitor of apoptosis protein (IAP) family proteins, are considered to be important in the regulation of intracellular caspase activation.[23–26] Activation of caspases is accelerated by Bax, but antagonized by Bcl-2 and Bcl-xL, which is regulated by the release of cytochrome *c* from the mitochondria. The activation of caspases, including caspase-3/-7/-9, is inhibited by IAP family proteins, where it acts downstream of cytochrome *c* release. XIAP expression was clearly downregulated by NF-κB inhibitors in our study, but the suppression of XIAP was markedly inhibited in HTLV-I Tax transfectants.[27] IAP family protein expression, including XIAP, is positively regulated by NF-κB,[28,29] and therefore part of the Tax-induced inhibitory effect toward apoptotic stimuli appears to be mediated by XIAP. The activation of caspase-8 is not inhibited by IAP family proteins. Therefore, although Bcl-2 expression was not changed in our study,[26] factors other than IAP family proteins could be involved in Tax-mediated antiapoptotic function. The importance of Bcl-xL in the antiapoptotic effects of HTLV-I infection has also been reported by other group.[30] Resistance to Fas-mediated apoptosis of peripheral T cells in HTLV-I transgenic mice with autoimmune arthr-

opathy has also been demonstrated.[31] Furthermore, a recent study has revealed the inhibitory action of Tax protein toward p53 function.[32] Taken together, the cells infected with HTLV-I are supposed to be resistant toward both death receptor-dependent and death receptor-independent apoptotic signals.

Involvement of other viruses in the development of RA and SS

A number of other candidate viruses, including Epstein–Barr virus (EBV) and parvovirus B19, have been investigated as suspected causative agents in the development of RA and SS. The localization of EBV DNA and EBV-associated antigens has been found in the synovial tissues of RA patients and the salivary glands of SS patients.[33–35] The increment of the copy number of EBV DNA in PB and salivary glands of SS patients has been demonstrated.[35] In addition, immunohistological examinations have identified the presence of EBV DNA and EBV-associated antigens such as latent membrane protein-1 (LMP-1) in the synovial tissues of RA patients.[33] The expression of human parvovirus B19 DNA and parvovirus B19-associated antigen, VP-1, has also been determined in the synovial tissues of RA patients.[36] VP-1 expression was found to be more prominent in the active synovial legions, and furthermore, parvovirus B19 was isolated from the RA synovial tissues.[36] These experimental results strongly suggest that EBV and parvovirus B19 trigger and/or perpetuate autoimmune/inflammatory processes in RA and SS. Cellular functions are also modulated by these virus infections. LMP-1 activates NF-κB nuclear translocation and increases the expression of Bcl-2.[37,38] EBV-coded BHRF-1 protein, a viral homologue of Bcl-2, is also reported to protect against human B cell apoptosis.[39] A nonstructual protein of parvovirus B19, NS-1, induces the activation of NF-κB, resulting in the activation of IL-6 gene expression.[40] Therefore, it is interesting to note that HTLV-I, as well as other viruses such as EBV/parvovirus B19, appears to activate the cells and/or protect the cells from apoptotic stimuli in a similar fashion. A few clinical and laboratory differences have been found between HTLV-I-seropositive and HTLV-I-seronegative SS patients, but the presence of in situ apoptotic cells and the expression of apoptosis-related molecules such as Fas/Fas ligand (FasL), mitogen-activated protein kinases, CD40/CD40 ligand (CD40L), Bcl-2-related proteins, and IAP family proteins was the same in these two groups of patients.[41–44] These results also showed the possibility that the causative agents of the HTLV-I-seronegative RA/SS in the patients in our study might be other viruses such as EBV or parvovirus B19.

Conclusion

We have shown in this review that HTLV-I is a candidate virus for the induction and/or progress of the disease processes of SS and RA. Epidemiological and virological examinations strongly suggest a close relationship between HTLV-I infection and SS/RA, but we could find no clear difference between HTLV-I-seropositive and HTLV-I-seronegative patients. These findings may imply that HTLV-I infection is one of many causative agents inducing SS and RA. In other words, cellular and humoral responses leading to the development of pathological manifestations of SS/RA could be the same, even though the cause, including HTLV-I infection, is different in each case. Nevertheless, human autoimmune diseases such as RA and SS arise from a small population of viral carriers, suggesting that other factors, such as the presence of certain HLA-DR haplotypes described in patients with RA infected with EBV,[45] might initiate the disease process. Further studies are needed to clarify the precise molecular mechanisms which induce SS and RA triggered by viral infections.

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