



Guest Editorial

HTLV-I/HTLV-II - A model for virus associated neuro-degenerative diseases

Two life threatening diseases are known to be etiologically associated with HTLV-I: the first described being the adult T cell leukemia/lymphoma (ATLL), as reported initially in Japan by Takatsuki *et al* in 1977 (Takatsuki *et al*, 1977), the second being the tropical spastic paraparesis/HTLV-I associated myelopathy (TSP/HAM), as we originally observed in 1985 in the French West Indies (Gessain *et al*, 1985).

Besides these two diseases for which a causal relationship has been established, there is a series of 'inflammatory' diseases or syndromes including polymyositis, arthritis, infective dermatitis and Sjögren disease for which an association exists, but its causal nature has not yet been established (Gessain, 1996). Last but not least, HTLV-I infection has been shown to accelerate the development and the severity of acquired immunodeficiency syndromes caused by HIV-1 (Bartholomew *et al*, 1987; Page *et al*, 1990).

HTLV-I and HTLV-II are transmitted in endemic developing countries mostly from mother to child by breast feeding, by sexual route in both endemic and epidemic areas, and mostly through blood exchanges in the occidental world. Infecting respectively the CD4 or CD8 cells, the HTLV-I and HTLV-II, after a few replicating cycles, may become latent in the organism for decades, sometimes life long. During their life time, 5–10% of antibody seropositive persons develop an associated disease (ATLL or TSP/HAM).

This lower pathogenicity of the oncoretroviruses (HTLV-I and II), as compared to the lentiretroviruses (HIV-1 HIV-2), is possibly linked to the fact that the HTLVs have been present for millenia, while the latter are recent in human populations. Molecular epidemiology and phylogenetic analyses of HTLV-I genomic subtypes permitted to observe a very high genomic stability of the HTLVs, and to detect geographical molecular HTLV-I subtypes possibly linked to migration of infected populations in the distant past (Gessain and de Thé, 1996).

Of interest for neuropathological pathogenesis, the two main routes of transmission, namely from mother to child by breast feeding in the developing world and through exchanges of blood by transfusion or needle sharing in the western world, do carry a specific risk for either ATL in the first

instance, or for TSP/HAM in the second instance. These two risk factors not prevailing in the developing world, environmental co-factors should play a crucial role in these areas to induce a reactivation of a life long latent retroviral infection, leading to HAM/TSP.

This issue, devoted to HTLV-I and neuropathology, contains two excellent reviews covering the virological and molecular aspects of neurological diseases induced by HTLV-I, by Gessain (pp 299–306) and by Wigdahl and Brady (307–322), respectively.

There follows a series of original contributions which bring interesting new light to the molecular aspect, the pathogenesis, the epidemiology and the treatment of TSP/HAM.

The observations by the group of Simona Ozden (Coscoy *et al* (pp 336–344)) that neurons are permissive to HTLV-I promoter expression on one hand, and that of Steve Jacobson (Fox *et al* (pp 323–329)) on the other hand, showing, by *in situ* hybridization, that TNF alpha was detected in spinal cord tissues, from autopsy of three out of three TSP/HAM patients in cells which were neither T cells, microglial cells nor macrophages, raise the possibility of a direct involvement of neurons in TSP/HAM viral pathogenesis.

The group of Yoshida (Saito *et al* (pp 330–335)) observed that the mutation rates in the non coding region of HTLV-I LTR in HAM/TSP patients were similar to those previously observed by the same group in the coding tax region, indicating that mutations in one gene correlate with mutations in other genes. Along the same lines, while we observed different rates of mutations in the LTR and pX regions (Komurian *et al*, 1991) the same geographical genomic subtypes could be characterized using either LTR or env sequences (Mahieux *et al*, 1997). On the therapeutic side, the Osame group (Nakagawa *et al*) reviewing the results of different clinical trials, on 200 patients with HAM/TSP conducted in his department between 1986 and 1993, came to the conclusion that immunomodulatory therapies have some beneficial effect on HAM/TSP, but that a specific therapy of HAM/TSP is not yet in hand. Lastly, two letters to the editor refer to epidemiological studies. The letter by Zaninovic *et al* (pp 357–360), involved the follow-up of 185 TSP

patients between 1981 and 1995, among whom 20% (37 cases) were persistently HTLV-I seronegative, with the same clinical symptomatology and course as the HTLV-I associated TSPs (HAM/TSP). This situation reminded us of the epidemics of TSP in Central Africa linked to famine due to drought with consumption of unduly prepared cassava roots containing cyanide (Rosling *et al*, 1988). Along the same lines, the situation described by Hassan *et al*, in Egypt indicating that out of 14 patients fulfilling the diagnosis of TSP in the neurologic department of Cairo University, only two cases were associated with HTLV-I.

Searching for environmental co-factors in different geographical areas when TSP are prevalent is therefore of critical importance to enlighten the pathogenesis of this neurological disease.

The severity of the two diseases etiologically related with HTLV, namely ATLL and TSP/HAM, together with the fact that HTLV-II is becoming epidemic among intravenous drug users in the western world (Feigal *et al*, 1991), raise the question of the necessity for an HTLV-I vaccine (de Thé *et al*, 1994). We do know from the animal oncoretroviruses field that RNA tumor virus vaccines are feasible and efficient to prevent either primary infection, or associated diseases, or both (de Thé, 1996). The high genomic stability of HTLV-I and the

existence of animal models in which protection against viral challenge has been successfully obtained by vaccination, represent favorable conditions for the development of an HTLV-I/II vaccine (Bomford *et al*, 1996). Different vaccine preparations are already available, including recombinant human vaccinia and avian pox viruses, adenovirus, all involving env sequences of HTLV-I.

An animal model is however missing for disease associated with HTLV-I (ATL or HAM) although rabbits heavily infected with HTLV-I immortalized cells eventually develop a massive polyclonal lymphocytosis. But such polyclonal immortalized cells do not represent leukemic cells as seen in ATLL. Further development of an animal model are in progress, especially in new-world monkey.

In summary there is no doubt that the HTLV-I/HTLV-II retroviruses represent not only an excellent model for virus associated neurodegenerative diseases, but raise problems of importance in public health.

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