The origin of Japanese HTLV-I

SIR—Gallo and his colleagues[1] seem still to believe that African blacks came to Japan with the Portuguese in the sixteenth century, that HTLV-I (human T-lymphotropic virus type 1) adult T-cell leukaemia virus was transmitted from them to the Japanese people and then became highly endemic in Japan[2,3]. But our studies[4,5] strongly suggest that HTLV-I was already present in aboriginal Japanese in prehistoric times.

There are at least three ethnically distinguishable populations in Japan: the Ainu in the north the Ryukyuans in the south and the Wajin, or "Japanese", inhabiting the rest of the country. In our examination of the prevalance of HTLV-I in these ethnic populations[4,6], we found that the incidence of virus carriers was highest in the Ainu and the Ryukyuans, not the Wajin, and that the seroprevalent frequencies in adults over 40 years old of these three ethnic groups were 45.2%, 33.9% and 1.1% respectively[4].

The Wajin, who constitute most of the present population of Japan, are considered to be descendents mainly of post-neolithic immigrants from the mainland in the Yayoi and the Kofun eras (300 BC to AD 600). The Ainu and Ryukyuans, who share several common physical and genetic traits, are considered to be relatively pure descendents of native Japanese populations. The Ainu in particular are regarded as descendents of the native population inhabiting mainly northern Japan from the pre-agricultural Jomon period, more than 2,300 years ago.

The highly endemic areas of the retrovirus in Japan have been demonstrated to be restricted to (1) the most northerly and southerly regions and (2) isolated areas in other regions[5,7,8]. These native populations have been relatively unaffected by the Wajin who are not HTLV-I carriers. In most other areas, however, the Wajin became predominant because of their higher technological skills, planting rice and making iron tools and arms, for example.

Gallo and his colleagues[1] state that "the Japanese word for monkey *amakawa* is... derived from the Portuguese word *macaco*, also meaning monkey, however, we do not call monkeys *amakawa*, but *saru*. Furthermore the Japanese word *amakawa* is derived from *Macao*, the Portuguese territory in China. It may be true that the Portuguese brought Africans and African monkeys to Japan, but there is no relation between the places where the Portuguese landed in Japan and the endemic area of HTLV-I[9,10]. Among the Ainu people living in Hokkaido (the most northerly island of Japan) there are no monkeys living outside zoos, HTLV-I is prevalent, but Roman Catholicism, which Gallo *et al.* say was imported from Portugal, is not. Thus, the hypothesis that Japanese HTLV-I derives from Africans brought by the Portuguese in the sixteenth century is inadequate. Alternatively, from our recent finding that HTLV-I is prevalent in northern Japan and the report of Gallo's group of the presence of HTLV-I carriers in the Arctic[11], we propose that, like simian HTLV-like virus, which is now found in Old World monkeys[12-14], HTLV-I was originally prevalent in all humans, but that during human evolution it was lost from all but a few populations.

Finally, we think that it is premature to draw a conclusion on the origins of HTLV-I, because many populations have not yet been examined.

T. ISHIDA

Primate Research Institute,
Kyoto University,
Inuyama, Aichi 484,
Japan

Y. HINUMA

Institute for Virus Research,
Kyoto University,
Sakyu-ku Kyoto 606,
Japan

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Phosphoinositol more than skin deep

SIR—Touqui *et al.* may have been too cautious in the discussion of their paper which showed that the phosphoinositol (PI) cycle is responsible for activation of phospholipase A_2 (PLA_2) and initiation of the arachidonic acid cascade in platelets[1]. Our current studies of epithelial growth control provide data that are in line with their hypothesis, allowing us to interpret the findings of the Paris group in a broader context. It has long been recognized that a tissue responds to injury in two ways — inflammation and regeneration — and that these are tightly coupled; indeed, in normal circumstances they are inseparable. From a teleological point of view this of course makes sense, but in mechanistic terms still awaits an explanation. We are now in a position to provide one, namely that both arms of the response are triggered by activation of the PI cycle.

As in certain other tissues, PLA_2 activity in human epidermis is calcium-dependent and appears to be inhibited by a lipocortin-like molecule[2]; the epidermal inhibitor also seems to be modulated by phosphorylation[3]. Thus the findings of Touqui *et al.* may be extended to epidermis, a conclusion strengthened by the report that phorbol myristic acetate increases the synthesis of arachidonic acid metabolites by cultured keratinocytes[4]. These metabolites include prostaglandins (responsible for vasodilation) and chemotactic agents, such as leukotriene B_4, which initiate invasion of the tissue by granulocytes.

The link with proliferation was originally suggested by observations that protein kinase C, following activation by diacylglycerol, phosphorylates (and hence activates) a membrane antiport which exchanges intracellular H^+ for extracellular Na^+. In several cell types the resulting increase in cytosolic *p*H causes entry of resting (G_0) cells into the mitotic cycle[5,6]. Again, extrapolation to epithelia seems reasonable, since phorbol esters applied topically to skin cause a dramatic hyperproliferation.

Further evidence comes from our unpublished observation that inhibitors of the antiport and/or protein kinase C, such as amiloride, abolish the recruitment of G_0 keratinocytes in human epidermis following experimental injury.

Thus the findings of Touqui *et al.* may well lead to a clearer understanding of the way in which a tissue responds to injury, one of the central problems in pathology. We would also note its relevance to psoriasis, a common skin disease with polygenic inheritance. The lesions of this disease are characterized by a continuous, chronic inflammation and secrete high levels of arachidonic acid metabolites[7]. The epidermis within the lesions is grossly hyperproliferative with a complete absence of G_0 cells[8] and PLA, activity increases in the entire epidermis of the patient which seems to result from an over-phosphorylation of the inhibitor[3]. It would seem that the PI cycle may be a rewarding field for research into the pathogenesis of this disease.

P.D. MIER
F.W. BAUER
R. HAPPLE

Department of Dermatology,
University of Nijmegen,
6524 M J Nijmegen,
The Netherlands

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