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A POSSIBLE ROLE FOR E-RECEPTOR IN IMMUNOSUPPRESSION IN LEPROSY

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Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* in humans. It exhibits a well defined clinical and immunological spectrum with two extreme polar forms—lepromatous (LL) and tuberculoid (TT) types. The former condition is a disseminated infection, with high bacterimia and much reduced cell-mediated immunity (CMI), while the latter is a resistant form with few bacilli in the lesions but with good CMI which is considered to be associated with protection (Godal, 1978; Nath, 1983; Bloom and Mehra, 1984). Generalized impairment of cellular immunity to mitogens and tuberculin purified protein derivative (PPD) is consistantly observed in untreated bacterial index positive (BI^+) LL patients and improvement on this immune status may occur after chemotherapy. However, anergy to *M. leprae* persists even after prolonged chemotherapy in BI^- LL patients. Therefore, it is considered that the lack of specific cellular immunity to *M. leprae* is the primary cause of the disseminated form of the disease (Godal et al, 1971; Talwar et al, 1972; Nath et al, 1977).

Several laboratories have been interested to elucidate the mechanism of this specific anergy in leprosy patients (Godal et al, 1971; Hirschberg, 1978; Mehra et al, 1980; Sathish et al, 1980; Salgame et al, 1983; Bloom and Mehra, 1984; Mohagheghpour, 1985).

The following are the major view points: (1) Lack of lymphocytes in circulation capable of responding to *M. leprae*, (2) Suppressor T-cells are responsible for inhibiting the CMI response to *M. leprae*, (3) adherent cell suppressor factors interfere with normal T-cell functions, (4) defective macrophage function and (5) T-cells of LL patients are unable to produce Il_2 and do not express Il_2 receptor. While these findings provide considerable information, the basic mechanism of the defect responsible for specific anergy in LL patients is yet to be elucidated.

Several workers have repeatedly expressed the view that the CMI defect in LL patients is specific to the antigens of *M. leprae*. However, this unresponsiveness could not exist to all the antigenic moities of *M. leprae*, since this organism shares several components with other mycobacteria

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(Harboe et al, 1977) and since these common antigens when derived from other mycobacteria do induce good CMI in LL patients, both *in vivo* and *in vitro* (Myrvang et al, 1973). This paradox has also been emphasized by Bloom and Mehra (1984). In other words, the 'specific' anergy is not due to the inability of LL patients to respond to given antigens of *M. leprae*, but because of the fact that these common antigens are presented by *M. leprae*. In fact, several studies referred above indicate that the generation of suppressor activity is *specifically* by *M. leprae*, but the immunosuppression generated is always non-specific.

Hypothesis :

It is proposed that the direct product(s) of *M. leprae* or the macrophage processed material derived from *M. leprae* when available in sufficient quantity in the micro-environment of immunocompetent cells would interact with the E-receptor (Sheep erythrocyte binding site) of T-cells in such a manner as to suppress the proliferative response of T-cells stimulated by antigens and mitogens. This results in the generalized or 'specific' immunosuppression depending on the bacterial load of the system from where lymphocytes are obtained.

Before enumerating evidences in support of this hypothesis, let me review briefly the present status of the role of E-receptor in immunoregulation. Human peripheral blood T-cells have a 50 KD glycoprotein on their surface, which binds specifically to sheep erythrocytes, thus forming rosettes (Verbi et al, 1982). This was in fact the earlier method to enumerate T-cells in humans. One of the monoclonal antibodies of OKT series (OKT11A) recognizes an epitope of the E-receptor (T11 complex) and their interaction prevents the formation of rosettes with sheep erythrocytes (Verbi et al, 1982). It also inhibits the proliferative response induced by mitogens (Con A) and antigens (PPD) as well as by Ca^{2+} ionophore A23187, but not by Phorbol-12-Myristate-13-Acetate (Palacios and Maza, 1982). The authors have interpreted these results to indicate that the interaction of OKT11A antibody with E-receptor gives rise to a signal which turns off the process of activation of T-cells. E-rosette formation (Gattringar and Wick, 1977; Verbi et al, 1982) and OKT11A binding on to T-cells are eliminated after trypsin treatment. Further, trypsin treated T-cells could no longer be inhibited by OKT11A from proliferation induced by PPD or Con A (Palacios and Maza, 1982).

With this background, let me review the experimental evidences in support of my hypothesis.

(1) Earlier studies, using the technique of E-rosette formation showed that the number of T-cells is significantly reduced in circulation of lepromatous patients in contrast to tuberculoid patients and normals (Dwyer et al, 1973; Jaswaney et al, 1980). However, after the advent of monoclonal antibodies, OKT3 has been used as a pan T-cell marker and consequently the reported findings indicate that there is no difference in the proportion of T-cells between the above two groups (Mshana et al, 1982). It must be mentioned here that OKT3 and OKT11A recognize different receptors on human T-cells (Verbi et al, 1982).

(2) In an earlier study, involving both untreated and treated LL patients, Nath et al (1977) have demonstrated that the number of early binding E-rosette forming cells (E-RFC) was significantly reduced in BI^{+} LL, but attained the normal level in BI^{-} LL patients after treatment.

(3) Another crucial evidence in support of this hypothesis would be to show the reduction in the number of immunofluorescence positive cells in peripheral blood of BI+ LL patients when reacted with OKT11A antibodies, in contrast to the normal level in the same individuals when the cells are reacted with OKT3 antibodies. Our recent study shows that OKT3+ cells were at the normal level, but the E-RFC/OKT11+ cells were significantly reduced in peripheral blood mononuclear cells (PBMC) of the same LL patients. Further, the number of $OKT11^{+}$ lymphocytes is significantly reduced by prior incubation of PBMC from normal subjects with *M. leprae;* however, the same treatment does not alter the proportion of $OKT3^{+}$ cells (Unpublished).

(4) On the basis of this hypothesis, one must expect a suppressive effect of *M. leprae* on PBMC of normal healthy contacts and TT patients. This is in fact true as evidenced by the findings that the *in vitro* proliferative response induced by PPD or PHA in PBMC of normal individuals was suppressed in the presence of *M. leprae* (either integral or sonicated preparation). The degree of suppression depends on the concentration and the time of addition of *M. leprae* to the lymphocyte cultures (Bjune, 1979; Touw et al, 1980; Bahr et al, 1981). Further there is a positive correlation between the kinetics of suppression by OKT11A and *M. leprae* derived material on the lymphoproliferative response induced by mitogen and antigen (Touw and Stoner, 1980; Palacios and Maza, 1982).

(5) The comparison can also be extended to the synthesis of interleukins in these two systems. Palacios and Martinez-Maza (1982) reported that OKT11A, by interacting with E-receptor prevented T-cells from acquiring

sensitivity to Il_2 and suppressed the production of Il_2 induced by mitogen or antigen. Similarly, a more recent study by Mohagheghpour et al (1985) demonstrated the same pattern of inhibition in the cultures of PBMC of LL patients in the presence of *M. leprae*.

(6) The above considerations would argue for the possibility that the T-cells obtained from the environment as presented by BI+ LL patients are already inhibited due to the interaction of the *M. leprae* derived factor with the E-receptor. If this is true, it should be possible to remove this 'block' by trypsin treatment. Our recent studies with the PBMC of LL patients support this contention (unpublished).

Finally, what is the nature of this *M. leprae* derived material which interacts with E-receptor on human T-cells? Not much could be said at present. Apparently, this factor is not prostaglandin, even though it could also be involved in non-specific immunosuppression in leprosy (Birdi et al, 1984). Lepromatous macrophages have been shown to synthesize in the presence of *M. leprae* a suppressive factor which is insensitive to indomethacin (Salgame et al, 1983; Nath et al, 1984). However, it is not known whether the above factor contains any component of *M. leprae*. Further, it is quite possible that the low level of proliferation induced by *M. leprae* even in TT patients and healthy contacts is due to the suppressive effect of *M. leprae* derived products (Smelt et al, 1978; Bjune, 1980). In fact, on the basis of a series of experiments, Touw and Stoner (1980) have suggested that the anergy in leprosy may be due to a direct inhibitory effect of *M. leprae* on the lymphocyte proliferative response, rather than to a particular cell type.

It is well known that a large number of cross reacting or common antigens are shared by different mycobacteria including *M. leprae*. It is also an accepted view that in the endemic area subclinical immunization presumably by these antigens provides protection to majority of people living in this area. Therefore, it is worthwhile to look for *M. leprae* derived material which binds to E-receptor of T-cells, as a possible mechanism for immunosuppression. In conclusion, it must be mentioned that the present hypothesis explains the end result of infection by *M. leprae*, culminating in disseminated form of leprosy but not the initial events or factors responsible for bringing in such a pathological condition. Further study in the family contacts would provide the answer to this question.

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