SUPPRESSION OF THE MIXED LYMPHOCYTE REACTION IN MAN BY A SOLUBLE T-CELL FACTOR
Specificity of the Factor for both Responder and Stimulator*

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We have previously reported the occurrence of suppressor T cells of the mixed lymphocyte reaction (MLR) in a human leukocyte antigen (HLA) Dw2 homozygous woman, J.H., who failed to respond to the allogeneic cells of her husband, W.H. (1, 2). When J.H. suppressor T cells were cocultured in MLRs between responder cells and unrelated, irradiated stimulator cells, they only inhibited the responses of individuals who shared the HLA-Dw2 specificity with J.H. Moreover, only when W.H. or a few other stimulator cell types were present was J.H. suppression of MLR responses detected. Thus, the J.H. suppressor T cell appeared to be specific for determinants in the irradiated stimulator cells as well as D locus products in the responder.

We now report that a soluble factor or factors, released into the supernate of the MLR by J.H. T cells, also mediates this suppression. Like the cell from which it is derived, the factor is highly specific for HLA-D products in the responder cell and partially specific for the W.H. stimulator cell.

Materials and Methods

Blood samples were obtained from a panel of healthy persons known to be homozygous or heterozygous for specific HLA antigens. All experiments were performed with lymphocytes isolated from fresh venous blood.

Preparation of MLR Supernates. As described previously (1, 2), mononuclear leukocytes from defibrinated blood were collected by Ficoll-Hypaque gradient centrifugation, washed, and then resuspended at 1 x 10^6 cells/ml in RPMI-1640 medium (Grand Island Biological Co., Grand Island, N.Y.) containing 100 U/ml penicillin, 100 μg/ml streptomycin, 2 mM glutamine, and 10% pooled type A human serum. Stimulating cells were irradiated in a 137cesium irradiator (Mark I model 24 irradiator; J. L. Shepherd, & Associates, Glendale, Calif.) with a dose of 6,000 rads to abolish their capacity to proliferate and to make the reaction unidirectional.

For preparation of suppressor factor, mixed lymphocyte cultures were carried out in loosely capped 15 ml round bottomed plastic test tubes (BioQuest, BBL, & Falcon Products, Becton, Dickinson & Co., Cockeysville, Md.) with 3 x 10^5 J.H. cells and 3 x 10^6 irradiated W.H. cells in a vol of 6 ml. Up to 10 replicate cultures were carried out simultaneously in air/5% CO2 at 37°C.

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1 Abbreviations used in this paper: HLA, human leukocyte antigen; MLR, mixed lymphocyte reaction; PBS, phosphate-buffered saline.
Control cultures consisting of J.H. cells alone (0.5 × 10⁸/ml) or J.H. and an unrelated irradiated cell (C.O.) were carried out simultaneously. After 48 h, the culture tubes were centrifuged at 400 g for 15 min at room temperature, after which the supernatant fluids were carefully withdrawn and pooled in 50 ml conical polypropylene tubes (Corning Glass Works, Science Products Div., Corning, N.Y.). To assure that no cells remained, pooled supernates were recentrifuged at 400 g for 15 min.

Assessing the Effects of Supernates on the MLR. To determine if the pooled supernates had any effect on the MLR, Ficoll-Hypaque enriched mononuclear leukocytes were suspended at 5 × 10⁶ per ml in RPMI-1640 medium supplemented as indicated above. 50,000 responder cells (0.01 ml) were cultured with 50,000 irradiated stimulator cells (0.01 ml) in round bottom microtiter trays (Linbro Chemical Co., New Haven, Conn.) with either 0.15 ml supplemented medium or 0.15 ml supernate. Cultures, prepared in triplicate or sextuplicate, were incubated in air/5% CO₂ for 6 days at 37°C. [³H]thymidine (New England Nuclear Corp., Boston, Mass.) was then added, 1 μCi per well, and the plates harvested in a Multiple Sample Harvester (MASH II, Microbiological Associates, Walkersville, Md.) 18 h later.

Separation of T Cells and B Cells. Peripheral blood mononuclear leukocytes were enriched for either T lymphocytes or B lymphocytes as previously described (1) on the basis of differential affinity for anti-immunoglobulin coated on plastic flasks. In this method 2 ml of Cohn Fraction II immunoglobulin (2 mg/ml) and soluble dicarbodiimide (1 mg/ml) in phosphate-buffered saline (PBS) were incubated in a 25 cm² polystyrene tissue culture flask (Corning Glass Works) for 1 h at room temperature. After the flask was washed with PBS-5% fetal calf serum, 2 ml of a 1:20 dilution of rabbit anti-human immunoglobulin was added and incubated for 30 min at room temperature before washing. Under these conditions monocytes as well as B cells adhered to the flask. The non-adherent T cells were decanted and the B cells removed after 2 h incubation at 37°C with RPMI-50% human A serum containing 1.25 mM EDTA. The T cells were measured in the two fractions by rosetting with sheep erythrocytes (1). The B cells were measured by staining with fluorescein-conjugated anti-Ig as described previously (3). Cell recovery was 75-90%, with T-cell fractions consisting of 85-90% rosetting cells and B-cell fractions consisting of 80-90% Ig-positive cells.

Results

Evidence that a Soluble Suppressor Factor is Released into the MLR Supernate by J.H. and that it is Specific for HLA Dw2 in the Responder. J.H. possesses the HLA antigens A2,3/B7,7/Dw2,2/DRw2,2. She shares no HLA antigens with her husband, W.H., who is HLA A11,28/B35,35/Dw1,-/DRw1,4. As shown in Table I, in the presence of medium alone, all of the responders tested proliferate vigorously in response to the irradiated stimulator, W.H. In the presence of supernate from a 48-h culture between J.H. and W.H., however, the responses of some donors were markedly inhibited. Of those individuals whose responses to W.H. were suppressed, all but one is positive for HLA-Dw2. The single exception is the cell R.K., which although not typed as HLA-Dw2 does share with J.H. the Dw2 associated Ia-like specificity DRw2, according to the criteria of the Seventh International Histocompatibility Workshop (B. Colome and R. Payne, personal communication).

Possession by responder cells of HLA-B7, an antigen in strong linkage disequilibrium with HLA-Dw2, is neither necessary for suppression nor sufficient for suppression in the absence of Dw2. For example, J.R., who is positive for Dw2 but negative for B7, is suppressed, but H.K., who possesses B7 but lacks Dw2, is not suppressed.

Results similar to those shown in Table I were obtained in five consecutive experiments in which 3 × 10⁶ J.H. cells were cultured with 3 × 10⁶ irradiated W.H. cells in a vol of 6 ml for 48 h. That is, a soluble suppressor factor was
Table I

The J.H. Suppressor Factor: Requirement for HLA-Dw2 in the MLR Responder Cell

| HLA  | A  | B  | Dw | DRw | Response to W.H. in the presence of J.H./W.H. supernate* | %Δ cpm |
|------|----|----|----|-----|----------------------------------------------------------|--------|
| C.L. | 2,3| 7,7| 2,2| 2,2| 43,847 ± 3,794                                          | 14,433 ± 1,451 | -67     |
| T.L. | 3,3| 7,7| 2,2| 2,2| 37,610 ± 4,599                                          | 11,112 ± 908  | -71     |
| T.L. | 3,3| 7,7| 2,2| 2,2| 81,683 ± 6,729                                          | 23,682 ± 2,399 | -71     |
| J.L. | 1,2| 7,8| 2,3| 2,3| 38,895 ± 3,076                                          | 20,684 ± 1,201 | -47     |
| R.L. | 1,2| 7,8| 2,3| 2,3| 20,818 ± 1,469                                          | 10,362 ± 1,368 | -50     |
| R.G. | 1,2| 7,8| 2,3| 2,3| 33,836 ± 2,065                                          | 17,073 ± 3,821 | -50     |
| J.R. | 1,10| 8,18| 2,3| 2,3| 66,953 ± 7,396                                          | 41,942 ± 4,722 | -37     |
| T.L. | 1,3| 7,7| 2,2| 2,2| 43,847 ± 3,794                                          | 14,433 ± 1,451 | -67     |
| W.B. | 2,29| 7,12| 2,7| 2,7| 24,610 ± 2,715                                          | 14,103 ± 916  | -43     |
| M.K. | 1,2| 21,35| 1,-| 1,-| 23,903 ± 3,316                                          | 30,773 ± 2,148 | +29     |
| C.O. | 1,2| 13,40| 1,-| 1,5| 48,945 ± 2,778                                          | 44,413 ± 2,060 | -9      |
| H.K. | 1,2| 8,7| 3,-| 3,7| 74,875 ± 4,110                                          | 67,550 ± 4,552 | -10     |
| C.H. | 1,2| 8,40| 4,6| 4,6| 37,025 ± 5,905                                          | 38,111 ± 4,827 | +3      |
| L.W. | 1,11| 8,35| 3,-| ND†| 80,316 ± 7,687                                          | 79,514 ± 9,376 | -1      |
| S.F. | 2,24| 13,27| 4,-| 4,5| 53,116 ± 6,255                                          | 58,976 ± 4,847 | +11     |
| D.B. | 9,14| 12,32| 4,-| 4,7| 27,366 ± 1,621                                          | 44,160 ± 2,910 | +61     |
| B.C. | 1,29| 17,35| 5,6| 5,6| 67,351 ± 7,549                                          | 73,590 ± 5,162 | +9      |
| D.S. | 3,29| 27,40| 5,-| 1,5| 29,641 ± 2,417                                          | 42,624 ± 4,705 | +44     |
| S.P. | 3,29| 21,12| 7,-| 3,7| 31,835 ± 2,131                                          | 29,538 ± 2,644 | -8      |
| R.K. | 1,28| 5,2| 14| ND†| 72,214 ± 5,550                                          | 54,440 ± 6,406 | -25     |

* Responses in cpm represent the means of six experiments ± standard error.
† ND, not done.

released into the supernate of the MLR, and this factor only inhibited the responses of Dw2-positive individuals. In earlier experiments, however, nonspecific suppression was observed in 96- and 144-h cultures and in 48-h cultures in which the concentrations of J.H. and W.H. cells had been increased fourfold (data not shown). No suppression was observed when an 18 h culture between J.H. and W.H. was tested (data not shown). On the basis of these observations we concluded that 48-h cultures between J.H. at 0.5 × 10⁶ cells/ml and W.H. at 0.5 × 10⁶ cells/ml were optimal for generation of specific suppressor factor. These conditions were duplicated in all subsequent experiments.

Antigen Specificity of the J.H. Suppressor Factor. We next tested the effects of the 48-h culture J.H./W.H. on the responses of the same donor panel to stimulator cells other than W.H. 10 such stimulators, chosen from a panel of HLA A, B, D typed cells, were tested. The responses of non-Dw2 individuals to these cells were not suppressed (data not shown). The effects of the same supernate on the responses of three Dw2-positive responders to these stimulator cells are shown in Table II. It is apparent that T.L., a cell homozygous for Dw2, is maximally suppressed in its response to W.H., although her responses to several other cells are also inhibited. Two Dw2 heterozygous responder cells are also inhibited maximally when W.H. is the stimulator cell and only slightly when other stimulator cells are tested.
TABLE II
Specificity of the J.H. Suppressor Factor for the Stimulating Cell in the MLR*

| Stimulator | Effect of the J.H. suppressor factor on mixed lymphocyte responses by: |
|------------|-------------------------------------------------------------------------|
|            | TL (Dw2,2)   | JL (Dw2,3)   | EG (Dw2,4) |
|            | %             | %             | %             |
| W.H.       | -71           | -47           | -54           |
| S.D.       | -57           | -27           | -7            |
| S.N.       | -46           | -11           | -32           |
| B.C.       | -42           | +3            | -6            |
| S.F.       | -58           | -3            | -10           |
| E.G.       | -33           | +8            | ND$           |
| L.W.       | -17           | +14           | +48           |
| H.K.       | +1            | +34           | +20           |
| W.B.       | +13           | +18           | +10           |
| C.O.       | -17           | +35           | +40           |

* Supernate from a 48-h culture between J.H. and irradiated W.H. cells was tested for the capacity to inhibit the responses of 3 Dw2-positive cells to a panel of 10 unrelated stimulator cells. Results are expressed as the % change (either inhibition [-] or enhancement [+] in baseline unidirectional MLRs.

$ ND$, not done.

TABLE III
Failure to Obtain J.H. Suppressor Factor in an MLR between J.H. and C.O.*

| Responder | Response to C.O. in the presence of: | Response to W.H. in the presence of: |
|-----------|---------------------------------------|---------------------------------------|
|           | J.H./C.O. Supernate                   | J.H./C.O. supernate                   |
|           | / % cpm                               | / % cpm                               |
| HLA       | Dw Medium                              | Medium J.H./C.O. supernate            | Medium J.H./C.O. supernate |
| C.L.      | 2,2 89,515 ± 7,833 99.977 ± 7.116     | +12 43,367 ± 3,204 62,898 ± 5,894     | +43 |
| T.I.      | 2,2 58,344 ± 4,967 76,963 ± 5,442     | +32 37,610 ± 4,805 38,435 ± 5,516     | +2 |
| R.L.      | 2,3 68,344 ± 6,338 86,963 ± 6,776     | +27 20,818 ± 2,081 24,272 ± 2,028     | +17 |
| E.G.      | 2,4 81,656 ± 6,372 115,075 ± 10,097   | +41 31,004 ± 1,927 37,727 ± 4,696     | +22 |
| W.B.      | 2,7 55,725 ± 6,073 61,012 ± 4,796     | +10 70,329 ± 6,551 83,381 ± 8,715     | +17 |
| M.K.      | 1,2 29,320 ± 3,745 39,416 ± 5,248     | +44 23,903 ± 1,905 34,708 ± 2,698     | +45 |
| H.K.      | 3,3 72,406 ± 6,699 94,234 ± 5,150     | +50 74,187 ± 7,414 76,187 ± 6,412     | +2 |
| S.F.      | 4,4 54,711 ± 4,550 70,403 ± 7,396     | +28 53,116 ± 5,328 62,371 ± 5,516     | +17 |
| B.C.      | 5,6 41,560 ± 4,440 77,136 ± 6,492     | +86 29,641 ± 2,760 40,943 ± 5,227     | +38 |
| S.P.      | 7,7 42,152 ± 5,512 66,473 ± 6,493     | +64 67,351 ± 5,100 92,222 ± 7,526     | +37 |

* Peripheral blood lymphocytes from J.H. were incubated for 48 h with irradiated C.O. cells (HLA A1,2/B13,40/Dw1,3/DRw1,5), and the supernate was tested for its capacity to suppress the MLR responses to C.O. and W.H. Results represent the mean of triplicate cultures ± standard error.

Effects of a Supernate Obtained from an MLR between J.H. and a Stimulator Cell other than W.H. It was of interest to determine whether or not generation of the J.H. suppressor factor required the presence of W.H. as the irradiated stimulator cell. Therefore, a 48-h supernate was prepared from an MLR between J.H. and an unrelated irradiated cell, C.O. (HLA A1,2/B13,40/Dw1,3/DRw1,5). As shown in Table III, this supernate not only failed to inhibit the responses to W.H. and C.O. but actually enhanced the responses of the entire panel to these stimulator cells. A 48-h supernate from J.H. cultured in the absence of other cells had no effect on the MLR responses of our panel (data not shown).

Evidence that the J.H. Suppressor Factor is Released by T Cells. 3 x 10⁶
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TABLE IV

Evidence that the J.H. Suppressor Factor is a T-Cell Product*

| Responder | HLA | Dw | %Δ Response to W.H. in the presence of: |
|-----------|-----|----|---------------------------------------|
|           |     |    | T-Cell supernate                      | B-Cell supernate |
| C.L.      | 2,2 | 2,2| –58                                   | –14             |
| T.I.      | 2,2 | 2,2| –41                                   | –12             |
| R.L.      | 2,3 | 2,3| –37                                   | –8              |
| E.G.      | 2,4 | 2,4| –39                                   | –9              |
| M.K.      | 1,- | +5 | +13                                   |
| H.K.      | 3,- | +2 | +12                                   |
| S.F.      | 4,- | +4 | +14                                   |
| B.C.      | 5,6 | +8 | +15                                   |

* Peripheral blood lymphocytes, enriched for either T cells or B cells, were incubated with irradiated W.H. cells for 48 h and the supernates tested for MLR suppressor factor. Results are expressed as % change (either inhibition [-] or enhancement [+]) in the base line unidirectional MLR.

J.H. T-enriched cells or B-enriched cells were cultured with 3 × 10⁶ irradiated W.H. cells in a vol of 6 ml for 48 h, and the supernates tested for suppressive activity. As shown in Table IV, significant suppression of Dw2 responders was obtained with supernate from a T-cell enriched culture but not supernate from a B-cell enriched culture.

Discussion

These results demonstrate that a soluble factor or factors suppressive of the MLR is generated when J.H. lymphocytes are cultured with the irradiated cells of her husband, W.H. Experiments with lymphocyte fractions enriched for either T cells or B cells suggest that the source of the J.H. suppressor factor is a T cell. J.H. T cells have been shown previously to inhibit the MLR (1, 2), and it is possible that the same cells are the source of suppressor factor.

The remarkable features of the J.H. suppressor factor are its specificity both for the MLR stimulator cell and for the MLR responding cell. The stimulator specificity parallels that observed with J.H. cells in MLR suppression (1, 2). The factor is generated in the combination J.H./W.H., and it is not generated when J.H. is cultured alone or with another irradiated cell, C.O. It suppresses the response to W.H. and certain other stimulator cells though these do not share HLA private specificities. In some instances suppression of the response to a broader spectrum of stimulating cells was seen (Table II).

The factor also shows specificity for the HLA-D region of the responding cell. The specificity is for HLA-Dw2, which is the HLA D type of J.H. A cell which lacked Dw2 but was nonetheless suppressed was serologically typed for the Dw2 associated Ina-like specificity, DRw2. These results, therefore, confirm the previous observation that sharing of D region products is required between the J.H. suppressor T cell and the target responder cell (2). This is the first report of such genetic restriction in immune cell interaction in man and the first example of a human T-cell factor that mediates such an interaction.
There are, however, a number of examples in mice. Thus, T-cell factors have been described that mediate interactions between T cells and T cells (4, 5), T cells, and B cells (6-8), and T cells and macrophages (9). Some murine T-cell factors are antigen specific (4, 8, 9, 10-12), and some only affect responders which share immune response region identity with the factor donor (4, 13). Although their exact nature is uncertain, it has been suggested that those factors which show antigen specificity may be related to the T-cell antigen receptor (14).

The murine factor described by Rich and Rich is similar to the J.H. factor in that it mediates suppression of the MLR and is generated by alloantigen-activated T cells (15). It is highly specific for responder cells in that it only affects the responses of strains histocompatible for the immune response region of the H-2 complex (to the right of and including I-C) (13). The murine MLR suppressor factor differs from the J.H. factor in its apparent lack of specificity for antigen (stimulating cell), but the range of specificity tested in inbred mice may be much less than in these experiments with outbred humans.

Experiments are in progress to determine both the target of the J.H. suppressor factor and the immunochemical nature of the factor. Antigen-specific factors in the mouse have been shown to have Ia antigen specificities (4, 8, 16-18). The presence of such specificities in the J.H. factor would add to the accumulating evidence that the HLA-D region in man is analogous to the murine immune response region.

Summary

J.H., an HLA-Dw2 homozygous multiparous woman, fails to respond to her husband, W.H. (HLA Dw1,-) in the unidirectional mixed lymphocyte reaction. T cells from J.H. were previously shown to suppress the responses of Dw2-positive cells but not Dw2-negative cells to W.H. We now report that a soluble factor released into the supernate of the mixed lymphocyte reaction by J.H. T cells, mediates this suppression. Like the cell from which it is derived, the factor is highly specific for HLA Dw2 in the responder cell and partially specific for the stimulatory alloantigen.

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