Roles of Murine Dendritic Cells and Macrophages in the Initiation of Primary Antibody Response *In Vitro*

II. Role of Macrophages as Modulators but Not as Accessory Cells

By

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Abstract. Accessory cell (A-cell) activity of murine dendritic cells (DC) and that of Ia-bearing macrophages (Ia$^+$ Mϕ) were investigated in the primary anti-sheep erythrocyte antibody response *in vitro*. Splenic DC manifested high A-cell activity. A-cell-depleted spleen cells supplemented with 1% DC developed a plaque-forming cell response to an extent comparable with the response of unfractionated spleen cells. However, peritoneal Ia$^+$ Mϕ, activated *in vitro* or *in vivo* by lymphokine, did not manifest significant A-cell activity. The Mϕ we employed represented strongly adherent Ia$^+$ Mϕ and, therefore, were free from such temporarily adherent Ia$^+$ non-Mϕ cells as DC. Furthermore, it was observed that both peritoneal Ia$^+$ Mϕ and Ia$^-$ Mϕ modulated the antibody response. The Mϕ occasionally appeared to enhance antibody response in the presence of insufficient number of DC and they suppressed the response in the presence of sufficient number of DC.

Introduction

The initiation of antibody response to a vast majority of antigens is mediated by so-called accessory cells (A-cells)[1]. The A-cell activity resides mainly in the adherent cell population (Mosier 1967, Roseman 1969, Shortman et al. 1970, Hoffmann 1970, Feldmann and Palmer 1971, Gorczynski et al. 1971, Chen and Hirsch 1972, Cosenza and Leserman 1972, Feldmann 1972, Pierce et al. 1974, Erb and Feldmann 1975, Lee et al. 1976, Chused et al. 1976, McDougal and Gordon 1977, Hodes et al. 1978, Nakano et al. 1978, Boswell et al. 1980), and there are many investigations indicating the participation of Ia-bearing (Ia$^+$) cells in the manifestation of A-cell activity (Hodes et al. 1978, Niederhuber 1978, Rosenthal 1978, Schwartz et al. 1978, Singer et al. 1979, Niederhuber and Allen 1980, Inaba and Muramatsu 1980).

Many immunologists have conceived that Ia$^+$ macrophages (Mϕ) "themselves" may be potent A-cells in primary antibody response (reviewed in Unanue 1981). However, we find no conclusive evidence for this assumption, since it seems possible that either the A-cell

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[1] Abbreviations: A-cell(s), accessory cell(s); DC, dendritic cell(s); EA, opsonized erythrocyte(s); Mϕ, macrophage(s); PEC, peritoneal exudate cells; PFC, plaque-forming cell(s); SAC, splenic adherent cells; SRBC, sheep erythrocyte(s).

or lymphocyte preparations employed by investigators who argued Ia$^+$ Mϕ as A-cells, contained Ia$^+$ non-Mϕ. For example, splenic adherent cells (SAC), which manifest high A-cell activity, comprise not only Ia$^+$ Mϕ and Ia$^-$ Mϕ but also Ia$^+$ non-Mϕ cells such as dendritic cells (DC) (Steinman and Cohn 1972, Steinman et al. 1979). The latter are known to manifest A-cell activity in two ways, in concert with Ia$^-$ Mϕ (Inaba and Muramatsu 1980, Inaba et al. 1981, 1982) and by themselves (Inaba et al. 1983a, b). It seems likely, however, that Ia$^+$ Mϕ in spleen are impotent as autonomous A-cells, since selective depletion of DC but not Ia$^+$ Mϕ from SAC with DC-specific monoclonal antibody plus complement ablated the primary antibody response (Inaba et al. 1983b). Thus, it is still uncertain whether Ia$^+$ Mϕ by themselves manifest A-cell activity as strong as DC.

In this paper, it is demonstrated that peritoneal Ia$^+$ Mϕ, activated *in vitro* or *in vivo* by lymphokine and carefully deprived of Ia$^+$ non-Mϕ cells such as DC, are weak or impotent A-cells under such a culture condition that DC play as potent A-cells. It is also shown that Ia$^+$ Mϕ as well as Ia$^-$ Mϕ modulate the manifestation of A-cell activity of DC. Preliminary study has already been published (Muramatsu et al. 1983).

Materials and Methods

Materials and methods employed in this study are the same as those described in the accompanying paper unless mentioned (Komatsubara 1985).

Mice—Inbred female C3H/HeSlc mice at the age of 2–4 months were used.

Spleen lymphoid cells devoid of A-cell activity—The yield was 14–31% of original spleen cells, and the constituents were as follows: 93.3–98.5% small lymphocytes, 0.16–5.4% polymorphs, and 0.97–1.8% morphologically identified blastoid cells of medium size. Mϕ and monocytes could not be detected. A small number of nonlymphoid adherent cells, however, differentiated from G-10-passed cells after the culture for 2 days or more, suggesting that the depletion of precursor cells of the adherent cells was not perfect. The number of adherent cells differentiating after 4 days of culture was 50–500 per 10^6 G-10-passed cells.

Dendritic cells (DC)—The yield was 0.08–0.19% of original spleen cells. Since Fc receptor-bearing cells could not be detected as opsonized erythrocyte- (EA-) rosetted cells, DC preparation seemed practically free from Mϕ. Contamination of blastoid cells was 0.18–0.56%, and Ia$^+$ cells were 90–93% when they were examined by complement-dependent cytotoxicity test.

CS Mϕ—CS Mϕ (CS$^+$, cultured in the presence of lymphokine; and CS$^-$, cultured in the absence of lymphokine) preparations were highly purified Mϕ populations. Yields of CS$^+$ Mϕ and CS$^-$ Mϕ were 50–65% and 41–50% of original PEC, respectively. 98.4–98.7% CS$^+$ Mϕ and 95.8–96.5% CS$^-$ Mϕ phagocytosed EA. More than 90% CS$^+$ Mϕ and less than 1% CS$^-$ Mϕ are Ia$^+$ under examination by indirect immunofluorescence technique (Naito et al. 1984). CS$^-$ Mϕ are not biologically inactive cells, since they express Ia antigens on their surface in the culture with lymphokine (Naito et al. 1984).

BCG-PEC—Four different preparations containing Ia$^+$ Mϕ to various degrees were employed. The constituents of whole PEC were as follows: 51.2–65.7% Mϕ and suspected DC, 2.3–29.1% polymorphs, 16.5–46.0% lymphocytes, and in some preparations, 0.07–0.4% mast cells. Yield of 2hAd PEC was 30–50% of whole PEC, and 50–70% were Mϕ. More than 95%

of the $M\phi$ were Ia$^+$.   Yield of 20hAd PEC was 20–30% of whole PEC, and 60–80% were $M\phi$. More than 95% of the $M\phi$ were Ia$^+$.   Yield of 20hNA PEC was 2–4% of whole PEC.   20–40% were $M\phi$, and 10–20% were non-EA-rosetted cells of dendritic morphology.

Splenic adherent cells (SAC)—SAC were prepared as described previously (Inaba et al. 1981). Briefly, spleen cells were incubated for 2–3 hr on plastic dishes, and nonadherent cells were removed by pipetting and aspiration.   The adherent cells were taken off by 0.6 mM EDTA, treated with anti-Thy 1.2 monoclonal antibody plus complement, irradiated with 1300 R X-ray, and cultured overnight in a dish with a bottom of Teflon film.   In the experiment of Fig. 3, 5×10^6 spleen cells were plated in a 24-well plate, incubated for 3 hr, and irradiated with 1300 R X-ray.   After removal of nonadherent cells, the adherent cells were used as SAC.

Evaluation of A-cell activity—A-cell activity was evaluated as the ability to elicit plaque-forming cell (PFC) response of A-cell depleted spleen cells (G-10-passed cells).   Culture was usually performed for 4 days in flat-bottomed 96-well plates. 10^6 G-10-passed cells were supplemented with cell population to be assessed for A-cell activity, and cultured with 10^6 sheep erythrocytes (SRBC) in 0.2 ml RPMI 1640 medium containing 5% FBS, 2 mM glutamine, 10 mM HEPES, 0.05 mM 2-mercaptoethanol, and antibiotics.   When $M\phi$ were cultured to evaluate their A-cell activity, the culture medium was also supplemented with 1 μg/ml indomethacin.   When culture was performed in 24-well plates, cell dose was 4–5 times as much as that in 96-well plates.   Antibody-forming cells were evaluated by PFC assay in agarose gel on slides (Jerne et al. 1963, Hosono and Muramatsu 1972).   Only the direct PFC method to assay IgM antibody-secreting cells was employed, since indirect PFC were seldom detected under this experimental condition.   The number of PFC in the culture without antigen was less than 20% of that with antigen.

Results

DC are potent A-cells

As shown in Fig. 1, DC manifested high A-cell activity without help from $M\phi$.   G-10-passed cells supplemented with various doses of DC were cultured in the presence or absence of SRBC in a flat-bottomed 96-well plate and anti-SRBC PFC were evaluated after 4 days.   G-10-passed cells supplemented with 1% SAC, which contained both DC and $M\phi$, were cultured as a positive control, and spleen cells were cultured as a reference.   G-10-passed cells alone did not develop PFC response whereas they developed high PFC response by supplementation with sufficient numbers of DC.   The response was comparable with that of the culture supplemented with 1% SAC.   PFC response without antigen was not significant (0–19 PFC).   Fig. 4 (cultured in 96-well plates) and Fig. 5 (24-well plates) also show similar results.   Since $M\phi$ were not detected in both DC and G-10-passed cell preparations (see Materials and Methods), these results strongly suggest that DC manifest high A-cell activity without help from $M\phi$.

Ia-bearing peritoneal $M\phi$ are impotent as A-cells

A.   *CS $M\phi$*—In the investigation of A-cell activity of CS$^+$ (Ia-bearing) $M\phi$, A-cell activity of CS$^-$ (non-Ia-bearing) $M\phi$ was also examined.   CS$^-$ $M\phi$ were employed as a negative control, since A-cell activity are known to reside in Ia$^+$ cells (Hodes et al. 1978, Niederhuber 1978,
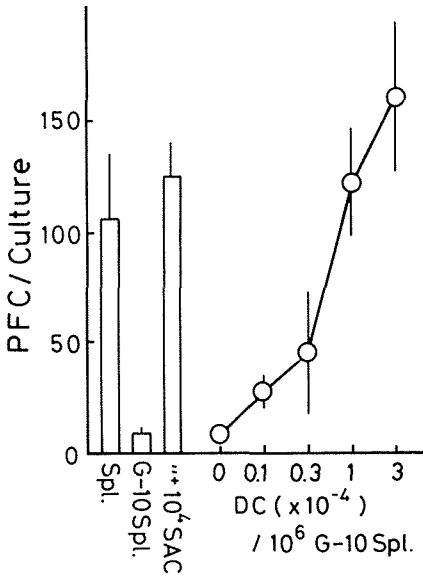
Fig. 1.   A-cell activity of DC preparation in *in vitro* primary anti-SRBC antibody response.   Cell number of whole spleen cells (Spl), and G-10-passed spleen cells (G-10 Spl) was 10^6.   Direct PFC per culture were evaluated after 4 days of culture in 96-well plates.   Each symbol and column represent the mean PFC number of quintuplicate cultures.   Vertical bars are SEM.

Rosenthal 1978, Schwartz et al. 1978, Singer et al. 1979, Niederhuber and Allen 1980, Inaba and Muramatsu 1980).

Investigations of A-cell activity of CS^+ Mϕ resulted in 3 cases: 1) no A-cell activity (Figs. 2A and 4B); 2) low A-cell activity which might not be due to the Mϕ, since the activity was independent of Ia-expression of CS Mϕ (Figs. 4A and 5A); and 3) suppression of PFC response (Fig. 5B).

In Fig. 2A, significant A-cell activity was not observed in CS^+ as well as CS^- Mϕ.   G-10-
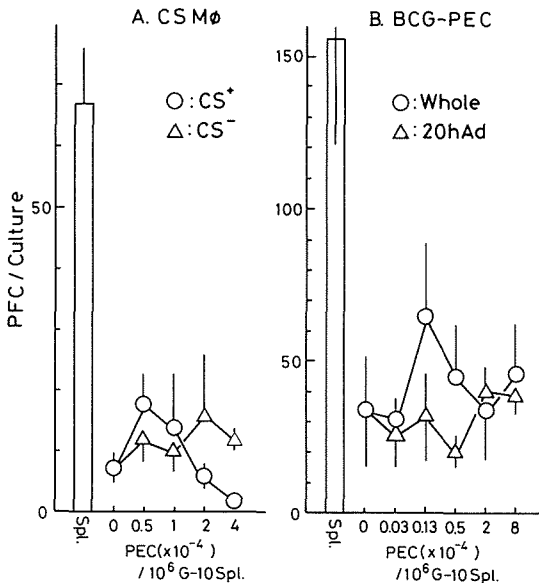

Fig. 2.   Examinations of the A-cell activity of CS Mϕ (A) and BCG-PEC (B).   The culture conditions were the same as those in Fig. 1.   Each symbol and column represent the mean PFC number of quadruplicate cultures.   The response of whole spleen cells is shown in each panel as a reference.

passed cells alone developed 7 PFC and when they were supplemented with $0.5-4 \times 10^4$ PEC (actual numbers of CS Mϕ were 41–65% of the plated PEC numbers; see Materials and Methods), they developed 2–18 PFC.

A-cell activity of CS Mϕ was compared with that of DC or SAC in 96-well plates (Fig. 4). In Fig. 4A, low A-cell activity was observed in 1% CS$^+$ Mϕ and 2% CS$^-$ Mϕ (62 and 63 PFC in G-10-passed cells plus respective CS Mϕ versus 28 PFC in G-10-passed cells alone), whereas DC manifested high A-cell activity even at a dose of 0.3% (109 PFC versus 28 PFC). 1% SAC also manifested high A-cell activity. In Fig. 4B, A-cell activity of CS Mϕ was not observed, whereas A-cell activities of DC and SAC were observed.

A-cell activity of CS Mϕ was also compared with that of DC in 24-well plates. The number of G-10-passed cells per well was 4 times as large as that in Fig. 4. In Fig. 5A, both 1 and 2% CS$^+$ Mϕ and 2% CS$^-$ Mϕ showed low A-cell activity, whereas 1% DC manifested high A-cell activity. In Fig. 5B, CS Mϕ did not manifest A-cell activity at all and they seemed suppressive. DC, however, manifested A-cell activity.

B. *BCG-PEC*—Whole PEC and 2hAd PEC manifested significant A-cell activity. The activity, however, did not seem to reside in most of the Ia$^+$ Mϕ of BCG-activated PEC, since an Ia$^+$ Mϕ-enriched preparation (20hAd PEC) did not manifested A-cell activity. In order to investigate A-cell activity of BCG-PEC, G-10 passed cells supplemented with various preparations of BCG-PEC were cultured in 96-well plates (Fig. 2B) or in 24-well plates (Fig. 3). The number of G-10 passed cells per well in 24-well plates was 5 times as large as that in 96-well plates. In Fig. 2B, whole PEC manifested low A-cell activity at a dose of 0.13%, whereas 20hAd PEC at doses of 0.03–8% did not manifest A-cell activity at all. 20hAd PEC at doses of 0.03–10% did not manifested A-cell activity also in Fig. 3, whereas 2hAd PEC manifested A-cell activity.

20hNA PEC manifested high A-cell activity (Fig. 3), and they contained two possible candidates for the A-cells: non-Mϕ cells of dendritic morphology (10–20%) and Mϕ (20–40%). The latter did not seem to be the actual A-cells, since Ia$^+$ Mϕ of 20hAd PEC did not manifested A-cell activity. If the actual A-cells in 2hAd PEC belong to the DC-like cells, they probably collaborate with Mϕ to manifest the A-cell activity, since they formed very minor part (0.4–2.4% of 2hAd PEC). It is also possible that some radioresistant T cells in 20hAd PEC, which escaped from the treatment with anti-Thy 1 antibody plus C, remained active to secrete lymphokines
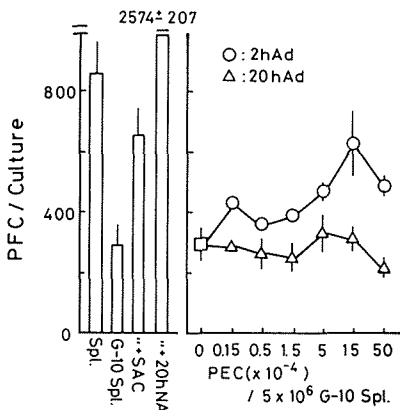

Fig. 3. Examinations of the A-cell activity of various BCG-PEC preparations. 2hAd PEC represented 2 hr adherent BCG-PEC. 20hAd PEC represented a subpopulation of 2hAd PEC which was still adherent after 20 hr. 20hNA PEC represented a subpopulation of 2hAd PEC which became nonadherent during 20 hr culture. SAC represented 3 hr adherent spleen cells, and were employed as a positive control. The culture was performed in 24-well plates for 4 days, and the number of whole spleen and G-10-passed spleen cells was 5×10^6. Each symbol and column represent the mean PFC number of triplicate cultures.
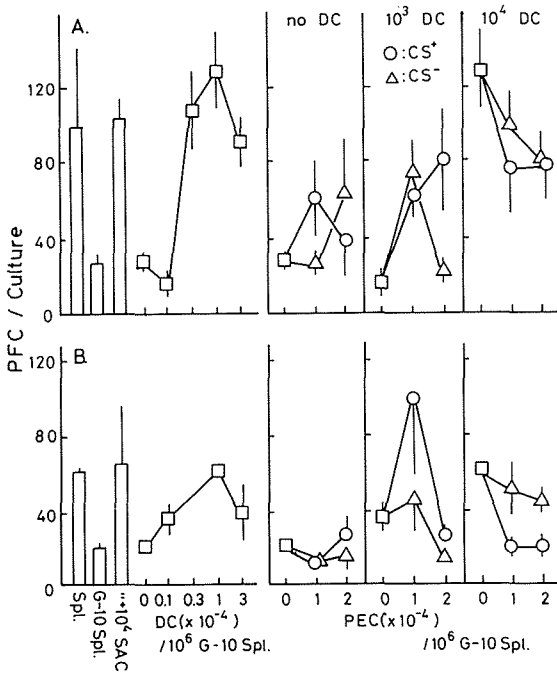
Fig. 4. A-cell activity of DC preparation and the modulatory effects of CS+ Mφ and CS- Mφ. (A) and (B) are results of separate experiments. The culture was performed in 96-well plates for 4 days, and the cell number of whole spleen cells and G-10-passed spleen cells was 10^6. Each symbol and column represent the mean PFC number of quadruplicate cultures.
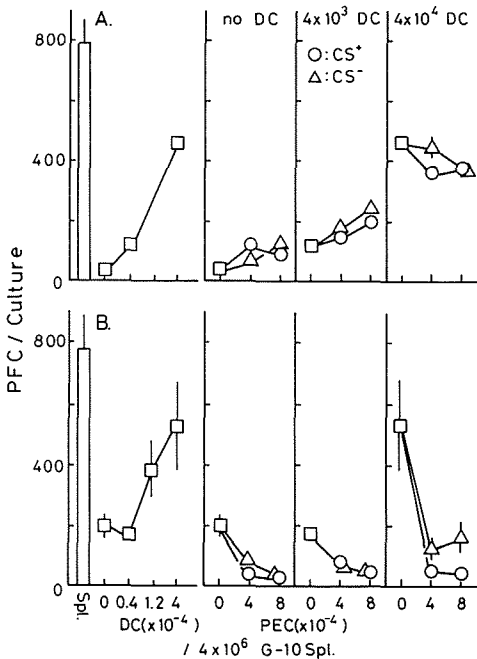

Fig. 5. A-cell activity of DC preparation and the modulatory effects of CS+ Mφ and CS- Mφ were examined in 24-well plates. (A) and (B) are results of separate experiments. Cell number of whole spleen cells and G-10-passed spleen cells was 4×10^6. PFC assay was performed after 4 days of culture. Each symbol and column represent the mean PFC number of quadruplicate (A) or triplicate (B) cultures.

which stimulated antibody response.   At any rate, it is necessary to purify these two populations in order to make any conclusion on the cell type of actual A-cells in BCG-PEC.

CS Mφ modulate antibody response

A.   *Modulatory activity of CS Mφ in the presence of high dose DC*—A high dose (1%) of DC manifested high A-cell activity.   When G-10-passed cells were cultured with 1% DC plus 1–2% CS Mφ (actual numbers of CS Mφ were about a half of the indicated PEC numbers), PFC response was suppressed to various degrees (10 independent experiments).   CS Mφ seemed to suppress the response independently of Ia expression, since CS⁻ Mφ as well as CS⁺ Mφ suppressed the response.   In 4 experiments, the suppression by CS⁺ Mφ appeared to be significantly higher than that by CS⁻ Mφ, suggesting that either Ia or the level of Mφ activation might play some roles.

B.   *Modulatory activity of CS Mφ in the presence of low dose DC*—Low dose (0.1%) DC did not manifest A-cell activity.   When G-10-passed cells were cultured with 0.1% DC plus 1–2% CS Mφ, PFC response resulted in 3 different cases: enhancement, suppression, and no altration. Nine independent experiments were performed and the results were as follows: the enhancement in 3 experiments (Figs. 4 and 5A); the suppression in 3 experiments (Fig. 5B, for example); and no alteration in 3 experiments (data not shown).

These complicated results may be due partly to the degree of inhibitory activity of CS Mφ employed.   Thus, it was easy to observe the enhancement of antibody response by CS Mφ in the presence of low dose DC when the suppression by CS Mφ was moderate in the presence of high dose DC, whereas the enhancement was not observed when the suppression by CS Mφ was eminent in the presence of high dose DC.

The enhancement was observed in both an Ia-dependent manner (Fig. 4B) and an Ia-independent manner (Figs. 4A and 5A).   It was not as conspicuous in Figs. 4A and 5A as in Fig. 4B, since both CS⁺ and CS⁻ Mφ moderately supported PFC response in the former figures.

Discussion

We have previously demonstrated that a non-Mφ cell population containing DC in a minor part does not manifest A-cell activity by itself, but the combination of it with Ia⁻ SAC resulted in the manifestation of high A-cell activity (Inaba and Muramatsu 1980, Inaba et al. 1981, 1982).   We proposed the cellular synergy between DC and Ia⁻ Mφ in the manifestation of A-cell activity.   However, the dose of DC seemed insufficient to evaluate A-cell activity of DC themselves.

In the present study, DC were prepared according to the method of Steinman's laboratory (Steinman et al. 1979, Nussenzweig and Steinman 1980).   As shown in Figs. 1, 4, and 5, DC manifested high A-cell activity without addition of Mφ to the culture.   Were the cell preparations contaminated by some Mφ?   We examined both the DC preparation and the G-10-passed cell preparation, resulting in no observation of such Mφ in both preparations.   We observed that some Mφ differentiated from G-10-passed cell preparation at later period of the culture, but it seems unlikely that such Mφ play a critical role in the manifestation of A-cell activity of DC since it is mostly at early period of the culture that A-cells are required in antibody response. Thus, it seems that DC manifest high A-cell activity without help from Mφ if sufficient numbers of

DC (0.3–1% or more) are employed, conforming to the results of Inaba et al. (1983a, b).

Thus, it seems reasonable to conclude that splenic DC are autonomous A-cells and the role of splenic Ia$^-$ Mϕ is the modulation of antibody response. Since SAC contain both DC and Mϕ, it seems quite likely that splenic Mϕ modulate the manifestation of A-cell activity when SAC are employed as an A-cell source. Mϕ seems especially important under such a condition that the number of DC is insufficient to manifest A-cell activity by themselves.

Do splenic Ia$^+$ Mϕ play as autonomous A-cells? We can not succeed to answer this question yet, since we can not prepare Ia$^+$ Mϕ population free from DC. Inaba et al. showed that selective depletion of DC but not Ia$^+$ Mϕ from SAC with DC-specific monoclonal antibody plus complement ablated the primary response, suggesting that Ia$^+$ Mϕ of SAC are impotent as autonomous A-cells (Inaba et al. 1983b). We have tried to deplete DC using the DC-specific monoclonal antibody (generously supplied by Dr. Steinman) plus complement several times and could have eliminated DC actually, but incompletely.

Do peritoneal Ia$^+$ Mϕ play as autonomous A-cells? In the present study, we demonstrated that peritoneal Ia$^+$ Mϕ, activated *in vitro* or *in vivo* by lymphokine (CS$^+$ Mϕ and 20hAd BCG-PEC respectively), did not manifest any significant A-cell activity under such a culture condition that DC played as potent A-cells. Thus, peritoneal Ia$^+$ Mϕ do not seem to play as autonomous A-cells. A crucial point to argue for this conclusion is that we employed cell populations which were practically free from DC.

Activated Mϕ are supposed to suppress antibody response as well as other immune responses (reviewed in Allison 1978). Are CS$^+$ Mϕ really impotent as A-cells, or do they have potentiality to manifest A-cell activity under such a culture condition that an inhibitory effect of Mϕ on lymphocytes can be eliminated? It has been reported that activated Mϕ secrete several mediators such as prostaglandins (PG) and H_2O_2 (Friedman et al. 1979, Drysdale and Shin 1981, Schultz et al. 1978, Nathan et al. 1979) which might suppress antibody response (Stenson and Parker 1980, Metzger et al. 1980). Thus, it is possible that the blockade of such mediators may result in the manifestation of A-cell activity of CS$^+$ Mϕ. However, this was not the case at least about PG and H_2O_2. In the experiments of Figs. 2, 4, and 5, 1 μg/ml indomethacin (an inhibitor of PG synthesis) was added to culture medium to prevent a possible inhibitory effect of PG which might be produced by CS$^+$ Mϕ. Addition of up to 10 μg/ml indomethacin did not alter the incompetence of CS$^+$ Mϕ to manifest the A-cell activity. Thus, the inhibition of PG synthesis did not seem effective. Furthermore, in the presence of 10^4 U/ml catalase (a scavenger of H_2O_2) and/or 5 μg/ml indomethacin, CS$^+$ Mϕ did not manifested A-cell activity (data not shown). Thus, it seems likely that CS$^+$ Mϕ, although they possess Ia antigens, do not act as autonomous A-cells.

Modulatory activity of CS Mϕ appears suppressive in most cases. However, in some experiments, both CS$^+$ Mϕ and CS$^-$ Mϕ enhanced antibody response in the presence of low dose DC which were insufficient to manifest A-cell activity by themselves. The enhancement mediated by CS Mϕ, however, was not so conspicuous as that mediated by splenic Ia$^-$ Mϕ which we have previously demonstrated (Inaba and Muramatsu 1980, Inaba et al. 1981). Since CS Mϕ were well-matured Mϕ, the maturation of Mϕ might lead to the decrease of the enhancing activity of CS Mϕ, or alternatively, to the increase of the suppressive activity of CS Mϕ.

We have recently demonstrated that peritoneal Ia$^+$ Mϕ are not autonomous stimulator cells in allogeneic mixed leukocyte reaction (MLR), but both Ia$^+$ Mϕ and Ia$^-$ Mϕ modulate the level of MLR (Muramatsu et al. 1983, Naito et al. 1984). Thus, Mϕ amplified the low level MLR to low dose DC and apparently suppressed the high level MLR to high dose DC.

We have also obtained similar results in the proliferative response of immune T cells, that peritoneal Ia$^+$ Mϕ are not autonomous A-cells, or antigen-presenting cells, but modulators (manuscript in preparation). It seems critical to remove Ia$^+$ cells from responder T cell population, since the contamination of Ia$^+$ non-Mϕ cells may result in the manifestation of A-cell activity by the synergy between Ia$^+$ non-Mϕ cells and Ia$^+$ Mϕ. Indeed, CS$^+$ Mϕ elicit the proliferative response of lymph node T cells purified by nylon wool and Sephadex G-10 columns. However, when the purified T cells are further treated with anti-Ia serum plus C to eliminate contaminating Ia$^+$ non-Mϕ cells, they no longer proliferate even in the presence of CS$^+$ Mϕ, although they proliferate well in the presence of DC.

Many investigators who have argued that Ia$^+$ Mϕ are principal A-cells in immune responses (reviewed in Unanue 1981) seems to employ cell populations containing Ia$^+$ non-Mϕ cells like DC. Therefore, it is very likely that they have observed the synergy between Mϕ and contaminating DC in the manifestation of A-cell activity, but not the A-cell activity of Ia$^+$ Mϕ themselves. For example, Lee and Wong have demonstrated that Mϕ derived from bone marrow (BM) cells by culturing in L-cell conditioned medium, manifest A-cell activity in POL-specific T-cell proliferative response (Lee and Wong 1982). When BM-derived Mϕ were fractionated according to size by velocity sedimentation and activated by lymphokine for 20 hr, Mϕ in any fraction were enhanced to express Ia antigens on their surface (18.7–51.1%). Enhancement of A-cell activity was observed mainly in smaller Mϕ fractions and larger Mϕ fractions were found suppressive at high doses (6–20%). Since DC seem to be also BM-derived cells (Steinman et al. 1974), it is critical to make clear whether the smaller Mϕ fractions contain non-Mϕ cells such as DC. Furthermore, as mentioned before, nylon wool-purified lymph node T cell preparations which they employed as a T cell source devoid of A-cell activity still seem to contain Ia$^+$ non-Mϕ cells which act synergistically with Mϕ to manifest A-cell activity in antigen-specific T cell proliferation (manuscript in preparation). Thus, it seems quite likely that they observed the synergy but not A-cell activity of the Mϕ themselves.

The synergy between DC and Mϕ seems essential in the elicitation of immune response under such a condition that the number of DC is insufficient to manifest A-cell activity by themselves. Most investigators who argue that Ia$^+$ Mϕ are principal A-cells do not seem to consider this point. For example, Tiele et al. presented the results suggesting that such a synergy between human DC and monocytes might occur in mitogen-triggered B and T cell response, although they interpreted their results as a evidence that DC were impotent as A-cells (Thiele et al. 1983). Since DC are a minority (1–2%) of adherent peripheral blood mononuclear cells (PBMC) (Van Voorhis et al. 1982), they seemed to evaluate the A-cell activity of low dose DC. Thus, the depletion of monocytes from PBMC resulted in the ablogation of mitogenic response of the PBMC, and supplementation of the monocyte-depleted PBMC with monocyte-enriched cell population restored the response.

Collectively, we have no evidence which argues that Ia$^+$ Mϕ are autonomous A-cells in immune responses examined so far, that is, in primary antibody response, primary allogeneic MLR, and secondary antigen-specific T cell proliferative response. Although Mϕ become to

express Ia antigens on their surface by lymphokine, such Ia$^+$ Mϕ do not seem to be autonomous A-cells.   The role of Ia$^+$ Mϕ, and also Ia$^-$ Mϕ, seems to be the modulation of immune response. Mϕ appear to modulate immune response, either positively or negatively, depending on the level of immune response elicited by Ia$^+$ non-Mϕ cells such as DC.

Acknowledgment

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