Adhesion Molecules on Human Myeloma Cells: Significant Changes in Expression Related to Malignancy, Tumor Spreading, and Immortalization

Catherine Pellat-Deceunynck, Sophie Barillé, Denis Puthier, Marie-José Rapp, Jean-Luc Harousseau, Régis Bataille, and Martine Amiot

Laboratoire d’Immunogénétique (C. P.-D., S. B., D. P., R. B., M. A.), InsERM U211, Institut de Biologie (M. A.), 9 Quai Moncousu et Département d’Hématologie (M.-J. R., J.-L. H.), Hôpital Dieu, 44035 Nantes Cedex 01, France

ABSTRACT

In order to evaluate putative changes of major adhesion molecule expression on plasma cells (PCs) associated with malignant transformation, tumor spreading, and immortalization, we have quantified and compared the expression of CD56, CD44, CD11a, CD49e, and CD45 RO/RA on normal PCs, malignant PCs from multiple myeloma patients in chronic phase, in accelerated phase with or without extramedullary progression, and from human myeloma cell lines. Plasma cell phenotype was defined with the use of two-color immunofluorescence in combination with B- or anti-CD38 antibodies. We found that all the adhesion antigens were expressed on normal PCs. Malignancy was characterized by an overexpression of CD56, whereas extramedullary spreading was associated with a dramatic down expression of CD56. Although CD44 remained unchanged, the subpopulation of PCs expressing CD11a, CD49e, and CD45RA/RO were significantly reduced during malignancy, and each of these negative subpopulations increased during disease acceleration. We demonstrated that CD11a and CD49e expression were correlated and defined the same subpopulation of PCs. The phenotype of HMCLs was similar to the expression profile of patients in accelerated phase with extramedullary spreading. In conclusion, we show that significant changes similar to the expression profile of patients in accelerated phase with or without extramedullary progression, and from human myeloma cell lines. Adhesion of HMCLs to BM stromal cells induced the secretion of IL-6 by BM stromal cells (11–13). IL-6 is the essential MM cell growth factor (14). The family of β1 and β2 integrin molecules contributed to these interactions, because mAbs against CD29, CD49d, and CD11a inhibited the induction of IL-6 secretion in the coculture of PCs with stromal cells (11, 12). The role of CD44 has been established in different systems: in mice the growth of primary plasmacytomas was shown to be dependent on CD44 physical contact with stromal cell feeder layers (15); and in humans the blockage of the CD44 interaction partly inhibited the adhesion of myeloma cells to stromal cells and the triggering of IL-6 by stromal cells (12). In the same context, we demonstrated recently that the interaction of myeloma cells with osteoblastic cells up-regulated the IL-6 secretion by osteoblastic cells through cell-cell contact. In addition to the interactions through CD49d and CD44, we provided evidence for CD56 involvement in the cellular contact between osteoblasts and myeloma cells. This observation is of interest because it has frequently been hypothesized that the lack of CD56 expression might play a role in the dissemination of the cells out of the BM (4, 16). All these data emphasized the critical role of the adhesion molecules expressed on myeloma cells for the cell-cell contact with the BM microenvironment. Moreover, it is conceivable that changes in the density or in the expression of these adhesion molecules could make possible the dissemination of PCs out of the BM. In that way, it appears important to quantify the changes in such major adhesion molecule expression in relation to malignant transformation, tumor spreading, and immortalization.

INTRODUCTION

MM is characterized by the proliferation of malignant PCs within the BM. The mechanisms by which malignant PCs migrate and localize in the BM have not been yet elucidated. Various studies have documented the expression of adhesion molecules on myeloma cell surface (1–6). A high expression of CD44, CD29, CD49d (VLA-4), and CD54 has been reported on normal and malignant PCs, in contrast to CD56 (NCAM) and CD58 (LFA-3), which were rather expressed on malignant PCs than on normal PCs. The expression of CD11a (LFA-1) on malignant PCs was shown to be associated with high tumor cell labeling index (7). On the other hand, Kawano et al. (8) have demonstrated that the expression of CD49e (VLA-5) distinguished two subpopulations, the CD49e+ cells, which were mature myeloma cells, and the CD49e− cells, which were proliferative immature myeloma cells. In addition, the expression of one or another CD45 isoforms (CD45RA and CD45RO) on PCs was shown to define different stages of differentiation, CD45RO being expressed on the most differentiated PCs (9, 10). Among these adhesion molecules, recent studies have demonstrated the functional importance of some of them in the interactions of myeloma cells with the BM environment. Adhesion of HMCLs to BM stromal cells induced the secretion of IL-6 by BM stromal cells (11–13). IL-6 is the essential MM cell growth factor (14). The family of β1 and β2 integrin molecules contributed to these interactions, because mAbs against CD29, CD49d, and CD11a inhibited the induction of IL-6 secretion in the coculture of PCs with stromal cells (11, 12). The role of CD44 has been established in different systems: in mice the growth of primary plasmacytomas was shown to be dependent on CD44 physical contact with stromal cell feeder layers (15); and in humans the blockage of the CD44 interaction partly inhibited the adhesion of myeloma cells to stromal cells and the triggering of IL-6 by stromal cells (12). In the same context, we demonstrated recently that the interaction of myeloma cells with osteoblastic cells up-regulated the IL-6 secretion by osteoblastic cells through cell-cell contact. In addition to the interactions through CD49d and CD44, we provided evidence for CD56 involvement in the cellular contact between osteoblasts and myeloma cells. This observation is of interest because it has frequently been hypothesized that the lack of CD56 expression might play a role in the dissemination of the cells out of the BM (4, 16). All these data emphasized the critical role of the adhesion molecules expressed on myeloma cells for the cell-cell contact with the BM microenvironment. Moreover, it is conceivable that changes in the density or in the expression of these adhesion molecules could make possible the dissemination of PCs out of the BM. In that way, it appears important to quantify the changes in such major adhesion molecule expression in relation to malignant transformation, tumor spreading, and immortalization.

MATERIALS AND METHODS

Patients. The expression of adhesion molecules has been studied in the BM of 49 patients with MM: they were 34 IgG, 11 IgA, and 4 pure Bence Jones only. The k:λ ratio was 1.28. Twenty-seven patients have been studied either at diagnosis (n = 23) or in the remission and plateau phase (n = 4). The diagnostic criteria of MM were those of the Southwest Oncology Group (San Antonio, TX) (17). Sixteen patients have been studied at the time of relapse or progressive disease due to primary treatment failures. Progressive disease was defined as follows: (a) >50% increase of monoclonal immunoglobulin above previous levels; (b) worsening anemia; and (c) occurrence of new lytic bone lesions. In vivo, it has been shown that the growth fraction of patients at diagnosis or remission was low, generally <5% (18). On the other hand, the growth fraction of patients with relapse or progressive disease was significantly higher, generally >20%. Thus, to simplify the presentation of the results: (a) patients at diagnosis or in remission were pooled and termed as in chronic phase; and (b) patients in relapse or with progressive disease were termed as in accelerated phase. Six patients in accelerated phase were in leukemic phase. They were termed as in the accelerated phase with extramedullary involvement.

The plasmocyte phenotype of MM patients always established on BM cells was compared to the plasmocyte phenotype of 12 healthy donors. Normal PCs were analyzed in BM cell populations (9 cases) and in tonsil cell populations (3 cases). For all the markers tested, normal PCs presented an identical
phenotype irrespective of their localization (tonsil or BM) except for CD44 as indicated later in the text.

**Human Myeloma Cell Lines and Culture Conditions.** Nine HMCLs were studied: LP1, L363, and OPM2 were purchased from DSM (Braunschweig, Germany); U266 and RPMI 8226 were obtained from American Type Culture Collection; the XG1, XG2, XG4, XG6, IL-6-dependent cell lines were established in the laboratory (19). Cell lines were maintained in RPMI 1640 culture medium supplemented with 5% of FCS, 2 mM glutamine, antibiotics (100 IU/ml penicillin and 100 μg/ml streptomycin) and 10 μM 2-β-mercaptoethanol. For the XG cell lines, 1.5 ng/ml of rIL-6 was added to the culture.

**Cell Preparations.** On the occasion of a diagnostic iliac crest puncture, 5–10 ml of BM aspirates were obtained, and BM mononuclear cells were isolated by Ficol-Hypaque centrifugation. Tonsils were obtained from subjects undergoing tonsillectomy. Adherent cells were then removed by allowing total mononuclear cells to adhere to a plastic flask in RPMI 1640–5% FCS for 90 min at 37°C in 5% CO2 humidified atmosphere; this short adherence did not allow any PCs to adhere to plastic. In addition, BM and tonsil cells from healthy donors were depleted of T lymphocytes by sheep erythrocyte resetting. The percentage of PCs in the total cell population ranged from 0.5 to 3% and from 3 to 85% for healthy donors and myeloma patients, respectively.

**Antibodies.** mAbs anti-CD44, anti-CD45RA, anti-CD38 directly conjugated to FITC, control IgG1-FITC, and control IgG1-PE were obtained from Immunotech (Marseille, France). Anti-CD45RO-FITC, anti-CD45RO-PE, and anti-CD11a-FITC were purchased from Dako (Glostrup, Denmark) and anti-CD56-PE from Becton Dickinson (Heidelberg, Germany). B-B4-FITC and anti-CD11a-PE were purchased from Innotest (Besançon, France). Purified B-B4 antibody was a gift from Dr J. Wijdenes (Innotherapie, Besançon, France). The anti-CD11a mAbs used were HHM104 (FITC conjugated) and B-B4a (PE conjugated). The anti-CD11a F(ab′)2 was a gift from Dr A. C. Bloem (University Hospital, Utrecht, Netherlands). Streptavidin conjugated to PE and to control were obtained from Immunotech and Sigma, respectively. Purified B-B4 and CD49e were biotinylated with the use of biotinamidoacapo N-hydroxysuccinimide ester (Sigma, St. Louis, MO) as described previously (16).

**Phenotypic Analysis of PCs.** The two-color immunofluorescence staining of PCs was done as described previously (16). Cells were analyzed on a FACScan flow cytometer (Becton Dickinson).

For two-color immunofluorescence, FITC-anti-CD44, FITC-anti-CD11a, FITC-anti-CD45RO, and FITC-anti-CD45RA were associated with PE-streptavidin-biotinylated B-B4, whereas anti-CD56-PE and anti-CD49e-biotin were associated with anti-CD38-FITC. When positive PCs represented >20% of the total PC population, we determined the level of positivity for each marker; we divided the mean fluorescence intensity of each marker by the fluorescence intensity ratio for each specific marker.

**RESULTS**

To investigate the PC phenotype, we took advantage of the technical approach that we described previously with the use of two-color immunofluorescence in combination with B-B4 or anti-CD38 antibodies (16). A representative two-color staining of myeloma cells (Fig. 1A) clearly demonstrated that all B-B4+ cells were located in the CD38 bright fraction and vice versa (see also Fig. 4E). We further confirmed that B-B4 mAb specifically stained PCs because all B-B4+ cells were cytoplasmic κ+ but λ− (the isotype of the monoclonal immunoglobulin of this MM patient was IgGk; Fig. 1, B and C). To compare the phenotype of malignant PCs at different stages of the disease, two parameters were analyzed for each patient: (a) the percentage of positive cells in the PC population; and (b) the fluorescence intensity ratio for each specific marker.

**CD56.** Although CD56 has been used to distinguish malignant from normal PCs, our recent study indicated that normal PCs expressed CD56 (4, 16). In the present study, we first confirmed that 10 of 11 healthy donors presented a CD56+ plasma cell subpopulation ranging from 10 to 100%. We next compared the percentage of CD56+–positive cells and the level of CD56 expression on normal and malignant PCs. As shown in Fig. 2A, malignancy (chronic and accelerated stage) led to a significant increase of the percentage of CD56+ cells in the PC population. Moreover, the m M was 12 for normal donors (n = 11), 52 for chronic MM (n = 25), and 44 for accelerated MM (n = 16), indicating that the level of CD56 expression was significantly enhanced during the malignant process [i.e., normal versus chronic (P < 0.01) or versus accelerated MM (P < 0.01); Fig. 3A]. No further significant differences could be observed between chronic and accelerated phases. However, the most striking finding was the loss of CD56 expression on BM myeloma cells from patients presenting an extramedullary involvement (m M = 1; n = 6; P < 0.01; Figs. 2A and 3A). These data confirmed that a strong association existed between the lack of CD56 expression and the spreading of malignant PCs out of the BM.

**CD44.** CD44 is a proteoglycan, which was shown to be implicated with tumor metastasis and extracellular matrix attachment (20–22). A large number of related isoforms derived from a single gene has been identified for CD44. In this study, to define the CD44 profile of expression on PCs we used an anti-CD44 mAb recognizing all CD44 isoforms. On normal PCs, CD44 was always expressed on all BM PCs (8 of 8 cases), whereas it was expressed on 70% of tonsil PCs (2 of 3 cases). On myeloma patients, most of malignant PCs expressed CD44 although about 20% of MM patients presented a large CD44-negative subpopulation (Fig. 2B). Also, 2 of 8 HMCLs were found negative for CD44. However, the level of CD44 expression during the different phases of MM did not show any significant changes (Fig. 3B; m M were 36 and 45 for chronic and accelerated phases, respectively). These results indicated that only 20–25% of MM patients presented a negative PC population for CD44.

**CD49e.** CD49e expression has been shown to distinguish proliferative immature myeloma cells (i.e., CD49e negative) from mature...
myeloma cells (i.e., CD49e positive). Normal PCs (9 of 10 cases) were positive for CD49e on a subpopulation ranging from 35 to 85%. Malignancy led to a strong decrease of the CD49e-positive subpopulation because the majority of MM patients in chronic or accelerated phases possessed <35% of positive PCs for CD49e (Fig. 2C). In terms of the percentage of positive cells, significant decreases were observed when comparing PCs from patients in accelerated phase with an extramedullary involvement to normal PCs ($P < 0.02$) or to PCs of patients in chronic phase ($P < 0.1$; Fig. 2C). The level of CD49e expression was not significantly different in healthy donors ($m_n = 22$), myeloma patients in chronic phase ($m_n = 16$), or in accelerated phase ($m_n = 20$) (Fig. 3C). HMCLs presented a CD49e expression profile similar to the patients with an extramedullary involvement ($m_n = 1$).

**CD11a**. As observed for CD49e, CD11a was always expressed in normal PCs: on a subpopulation of normal PCs (7 of 10 cases) or on all the PCs (3 of 10 cases; Fig. 2D). Representative CD11a expression profiles analyzed by two-color immunofluorescence in combination with B-B4 antibody are presented in Fig. 4, C and F, for normal and malignant PCs, respectively. As shown in Fig. 2D, a significant decrease of the percentage of positive cells ($P < 0.01$) was correlated with malignancy (normal versus chronic $P < 0.01$). By consequence, the $m_n$ decreased from 19 (healthy donors) to 4 (chronic MM) and finally to 1 for accelerated MM (Fig. 2D). Analysis of the $m_n$ of CD11a expression during the different phases of the disease could not show any significant modifications. HMCLs presented an identical profile for CD11a to patients in accelerated phases [i.e., a lack of expression ($m_n = 1$); Fig. 3D].

**CD11a and CD49e Expressions Were Correlated on Malignant PCs.** Because the proportion of the PC subpopulation expressing CD11a and CD49e decreased on malignant PCs, we next investigated whether there was a correlation between these two parameters. On a large panel of 47 MM patients, a strong positive correlation was found between the expression of CD11a and CD49e on malignant PCs in terms of the percentage of positive cells. The correlation coefficient was $r = 0.70$ ($P < 0.001$; Fig. 5).

To investigate more directly the coexpression of these antigens on individual malignant PCs, a three-color immunofluorescence analysis was performed with the use of anti-CD11a, anti-CD49e, and B-B4 antibodies. For this purpose, CD11a and CD49e immunofluorescences were analyzed on the restricted B-B4-positive population. A healthy donor and three patients have been analyzed, and representative cytograms of one of these patients are presented in Fig. 6. As illustrated, most of the PCs (>92%) were either positive or negative for both CD11a and CD49e. In consequence, very small CD11a−CD49e+ and CD11a+CD49e− subpopulations were observed. Similar results were obtained for the healthy donor and for the two other patients (data not shown) demonstrating that a close correlation existed between the CD11a and the CD49e expression on PCs.

**CD45RO and CD45RA.** Previous studies indicated that the differentiation of B cells toward PCs is characterized by the loss of CD45RA isoform expression and the simultaneous acquisition of

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Fig. 2. Expression of adhesion molecules in terms of percentage of positive cells on normal and malignant PCs. Horizontal lines, median of positive cells within each given specific marker and group of patients. M, medullary; EM, extramedullary.
Fig. 3. Expression of adhesion molecules in terms of fluorescence intensity ratio on normal and malignant PCs. Horizontal lines, median of fluorescence intensity ratios within each given specific marker and group of patients (mn). M, medullary; EM, extramedullary.

Fig. 4. Immunofluorescence profiles of CD11a on normal and malignant PCs. Human BM cells were isolated from BM aspirates from one healthy donor (A, B, and C) and one MM patient in chronic phase (D, E, and F). Two-color analysis of BM cells with anti-CD38-FITC and B-B4-biotin-streptavidin-PE (B and E) and with anti-CD11a-FITC and B-B4-biotin-streptavidin-PE (C and F) is shown. The corresponding controls with an irrelevant antibody are shown in A and D.
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CD45RO (9, 10). On normal PCs, CD45RA and CD45RO were expressed on large subpopulations in most of the cases (illustrated in Fig. 2, E and F): the level of expression was 15 for CD45RA and 18 for CD45RO. On malignant PCs, both the level of expression and the percentage of positive cells for CD45RA and CD45RO were reduced significantly [chronic versus normal (P < 0.01)], but no additional significant differences could be observed during the subsequent stages of the disease (Figs. 2, E and F and 3, E and F).

CD45RA and CD45RO Expressions Were Correlated on Malignant PCs. Because CD45RA and CD45RO showed similar modification of expression during the different stages of the disease, we then analyzed the correlation between these two markers in terms of percentage of positive cells on malignant PCs. Twenty-eight couples were analyzed, and the correlation coefficient was 0.76, indicating a very high correlation between the expression of CD45RA and CD45RO (P < 0.001; Fig. 7). To confirm the coexpression of CD45RA and CD45RO on a single PC, a three-color staining was performed with the use of anti-CD45RA, anti-CD45RO, and B-B4 mAbs. Fig. 8 shows representative cytograms of one MM patient for the CD45RA and CD45RO expression on the gated B-B4-positive population. The results demonstrated that a small proportion of malignant PCs for this patient expressed CD45RA (5%) or CD45RO (7%) (Fig. 8, A and B). The cytogram C reveals the existence of all four subpopulations CD45RA⁺CD45RO⁻, CD45RA⁻CD45RO⁺, CD45RA⁺CD45RO⁺, and CD45RA⁻CD45RO⁻. In conclusion, we demonstrated the existence of a PC subpopulation expressing CD45RA and CD45RO.

DISCUSSION

In MM, PCs remain located essentially within the BM and rarely disseminate outside the BM, except in the terminal stage of the disease. A better understanding of the expression of adhesion molecules and of their quantitative changes during the different stages of the disease may be critical for defining the mechanisms by which the PCs adhere to or detach from the BM environment.

With regard to the CD56 expression, we confirmed that CD56 was expressed on normal PCs, up-regulated on myeloma PCs, and down-regulated on BM PCs from patients with an extramedullary involvement. The PCs from patients with an extramedullary involvement were also analyzed in the extramedullary site (blood), and we observed that they shared the same CD56⁻ phenotype as the BM PCs (results not shown). These findings extend and confirm our recent report indicating that the loss of CD56 occurred in the BM and was correlated with the capacity of cells to disseminate out of the BM. Because we demonstrated recently that osteoblastic cell lines interact with myeloma cells through CD56, it is conceivable that the overexpression of CD56 on myeloma cells favors the capacity of adherence of myeloma cells to the osteoblastic cells. Among the hematopoietic disorders, two presented a very particular CD56 expression profile on malignant cells (23, 24). Indeed, an abnormal expression of CD56 has
been underlined on some chronic myeloid leukemia, and among the T-large granular lymphocyte leukemia, those expressing CD56 identified aggressive variant of this leukemia. Although the function of CD56 remains unknown, in all of these disorders CD56 appears to be an important biological marker probably involved in the adhesive mechanisms and tumor cell dissemination.

As reported previously, we found that the normal PCs expressed CD49e on a large subpopulation (8). On malignant PCs, we observed an important decrease of positive subpopulation although the number of CD49e molecules expressed on the cell surface was not significantly modified. This result is in favor of the disappearance of the positive subpopulation. The absence of CD49e expression on most HMCLs and on PCs from patients with an extramedullary involvement suggested a relationship between the lack of CD49e and the increase of the plasmablastic compartment in the PC population. These observations find counterpart in the study of Kawano et al. (8), which demonstrated that CD49e- myeloma cells were proliferative immature cells, whereas CD49e+ cells were mature myeloma cells.

In contrast to CD49e, CD49d was always expressed on all normal and malignant PCs (results not shown), and this finding is compatible with the importance of CD49d in the terminal B-cell differentiation and with its involvement in the immunoglobulin secretion of PCs (25).

In this study, we demonstrated that CD11a expression was detected on a subpopulation of normal PCs, the percentage of this subpopulation ranging from 20 to 100%. This finding is in disagreement with one previous report and may be explained by the difference in the sensitivity of the detection methods (microscopy versus fluorescence-activated cell sorting analysis; Ref. 7); the differences are not supported by differences in the staining due to the mAbs used because we obtained the same results with 2 mAbs (MHM24 and B-B4). Moreover, the staining of HMCLs with the three anti-CD11a mAbs (MHM24, B-B4, and F8.8) was similar (data not shown). As observed for CD49e, the CD11a+ subpopulation decreased during malignancy but the level of the intensity per positive cell was not significantly changed. In human lymphoma, it has been well documented that the absence of CD11a was related to the aggressiveness of the lymphoma (26–29). Our results on malignant PCs are consistent with this finding. Moreover, we demonstrated that the percentage of CD11a-positive PCs was well correlated with the percentage of CD49e-positive cells in the malignant cell population, and by three-color immunofluorescence we confirmed that CD11a and CD49e were expressed on the same subpopulation of PCs. On the basis of our data and the results of Kawano et al. (8) concerning CD49e, it is believed that the lack of CD11a could be related with the proliferative immature PCs. The lack of CD11a and CD49e expression on most of the myeloma cell lines is in good agreement with this hypothesis.

In the present report, we also described the expression of two isoforms of CD45 that were expressed on restricted populations of normal and malignant PCs. The reduction of expression of both CD45RA and CD45RO on PCs is correlated with malignancy. Moreover, by three-color staining, we provided evidence of the existence of a subpopulation expressing both CD45RA and CD45RO. This finding is in agreement with the observation that a close correlation existed between the expression of CD45RA and CD45RO on malignant PCs. Taken together, our results seem to exclude a putative transition in CD45 isoform expression in relation with the stage of maturation of the PCs. The phenotype of HMCLs is in good agreement with this hypothesis because the large majority of these cell lines were CD45RA- and CD45RO-. According to the changes observed for the individual adhesion molecules during the different stages of MM, general characteristics associated with malignant transformation and tumor spreading can be proposed. Malignancy was characterized by a strong overexpression of CD56 in terms of both number of PCs expressing CD56 and number of CD56 molecules present on the cell surface. This overexpression of CD56 was associated with a decrease of the proportion of PCs expressing CD11a, CD49e, and CD45 RO/RA, whereas CD44 remained unchanged. Disease acceleration within the BM was not significantly different of the chronic phase. Extramedullary spreading was associated with a dramatic down-expression of CD56 in association with a decrease of CD11a+ CD49e+ and CD45 RO+/RA+ subpopulations but no significant modification of the level of CD44 expression. Normal PC population always presented negative subpopulations for the antigens CD11a, CD49e, CD45RA, and CD45RO that could identify the same subpopulation. By consequence, we can propose that this compartment increased in relation with the malignancy and could be a good indicator of disease aggressiveness. Furthermore, we can notice that CD44 and VLA-4 expressions, which were not significantly modified during MM, were also the antigens that did not define subpopulation on normal BM PCs.

The loss of several adhesion molecules may reduce the cell-cell interactions, and it is tempting to speculate that these cells escape more easily to the immune surveillance and present a selective advantage of proliferation. Finally, the variations of the adhesion profile phenotype presently described are easily quantified and could be of diagnostic and prognostic value in individuals with MM.

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REFERENCES


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