Cardiovascular dysfunction caused by cecal ligation and puncture is attenuated in CD8 knockout mice treated with anti-asialoGM1

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Tao, Weike, Victor T. Enoh, Cheng Y. Lin, William E. Johnston, Peng Li, and Edward R. Sherwood. Cardiovascular dysfunction caused by cecal ligation and puncture in CD8 knockout mice treated with anti-asialoGM1. Am J Physiol Regul Integr Comp Physiol 289: R478–R485, 2005. First published April 21, 2005; doi:10.1152/ajpregu.00081.2005.—The present study was designed to assess hemodynamics and myocardial function at 18 h after injury caused by cecal ligation and puncture (CLP) in CD8-knockout mice treated with anti-asialoGM1 (CD8KO/αAsGM1 mice). Arterial pressure was measured by carotid artery cannulation, and left ventricular pressure-volume measurements were obtained by use of a 1.4-Fr conductance catheter. Blood acid-base balance and indexes of hepatic, renal, and pulmonary injury were also measured. CD8KO/αAsGM1 mice exhibited higher mean arterial pressure and increased systemic vascular resistance compared with wild-type mice. Cardiac output was significantly decreased in wild-type, but not CD8KO/αAsGM1, mice compared with sham controls. Myocardial function was better preserved in CD8KO/αAsGM1 mice as indicated by less impairment of left ventricular pressure development over time, time varying maximum elastance, end-systolic pressure-volume relationship, and preload recruitable stroke work. The impairment in myocardial function was associated with induction of proinflammatory cytokine mRNAs in the hearts of wild-type mice. The hemodynamic derangements in wild-type mice were coupled with significant metabolic acidosis and elevated serum creatinine levels. Overall, this study shows that cardiovascular collapse and shock characterized by hypotension, myocardial depression, low systemic vascular resistance, and metabolic acidosis occurs after CLP in wild-type mice but is attenuated in CD8KO/αAsGM1 mice. These observations likely explain, in part, the previously observed survival advantage of CD8KO/αAsGM1 mice following CLP.

blood pressure; vascular resistance; cardiac output; left ventricular function; perfusion

β2-microglobulin knockout mice treated with anti-asialoGM1 (β2M/αAsGM1 mice) exhibit improved survival after cecal ligation and puncture (CLP) compared with wild-type mice (19). This survival benefit is associated with less hypothermia, decreased metabolic acidosis, attenuated systemic inflammation, and preserved cardiovascular function (19, 23). However, β2MKO/αAsGM1 mice have multiple immunological defects including an absence of CD8+ T, natural killer (NK), and natural killer T cells as well as deficient expression of the class I major histocompatibility complex and CD1 molecules (2, 15, 17). One of our goals has been to determine which of these immunological alterations confers resistance to CLP-induced injury. Our recent studies indicate that depletion of CD8+ T and NK cells is a major factor in this regard. Adoptive transfer of CD8+ T and NK cells into β2MKO/αAsGM1 mice will reestablish CLP-induced mortality (19). More recently, we showed that mice specifically depleted of CD8+ T and NK cells exhibit improved survival and decreased systemic inflammation after CLP compared with wild-type controls (18). The survival benefit observed in CD8+ T and NK cell-deficient mice was comparable to that observed in β2MKO/αAsGM1 mice. However, the physiological factors associated with improved survival in mice specifically depleted of CD8+ T and NK cells remain to be determined.

Hemodynamic alterations and cardiac contractile dysfunction are key manifestations of injury caused by CLP. Our laboratory (22) reported studies on hemodynamic function in mice after CLP and showed that wild-type mice exhibit significant hypotension associated with myocardial depression and decreased systemic vascular resistance. In a subsequent study (23), our laboratory showed that β2M/αAsGM1 mice exhibit improved myocardial function, increased systemic vascular resistance, and less hypotension than wild-type mice after CLP. On the basis of these observations, we hypothesized that mice specifically depleted of CD8+ T and NK cells would be resistant to cardiovascular dysfunction after CLP. We chose to examine mice depleted of both CD8+ T and NK cells because our previous studies have shown that depletion of NK cells alone does not improve survival after CLP and that isolated CD8+ T cell depletion provides only marginal benefit (18). Removal of both CD8+ T and NK cells causes decreased inflammation and improved survival that is far beyond that observed with depletion of either cell population alone. To test our hypothesis, we utilized the conductance catheter model of hemodynamic monitoring to assess cardiovascular function and myocardial contractility in CD8+ T and NK cell-depleted mice after CLP. In addition, CLP-induced myocardial inflammation, acid-base balance, and indexes of kidney, liver, and lung injury were measured.

MATERIALS AND METHODS

Mice. Female, 6- to 8-wk-old C57BL/6J and CD8 knockout (CD8KO, strain B6.129S2-Cd8atm1Mac) mice were purchased from the Jackson Laboratory (Bar Harbor, ME). NK cells were depleted by treatment of mice with anti-asialoGM1 (50 μg ip; Cedarlane Labora-

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CLP. Mice were anesthetized with 2% isoflurane in oxygen via facemask. A 1- to 2-cm midline incision was made through the abdominal wall; the cecum was identified and ligated with a 3-0 silk tie 1 cm from the tip. Care was taken not to cause bowel obstruction. A single puncture of the cecal wall was performed with a 20-gauge needle. The cecum was lightly squeezed to express a small amount of stool from the puncture site to ensure complete perforation. The cecum was returned to the abdominal cavity, and the incision was closed with a continuous suture. Mice received 2 ml of lactated Ringer’s solution subcutaneously in the dorsal area for fluid resuscitation. Sham mice underwent anesthesia, laparotomy, and wound closure but were not exposed to the CLP procedure. Sham procedures were performed on both wild-type and CD8KO/asGM1 mice. Hemodynamic measurements were performed at 18 h after sham or CLP procedures in wild-type and CD8KO/asGM1 mice. This time point was chosen because wild-type mice exhibit significant inactivity and physical evidence of CLP-induced morbidity but do not exhibit mortality until 24–30 h after CLP.

Left ventricular pressure-volume and systemic blood pressure measurements. Mice were anesthetized with 2% inhaled isoflurane in oxygen as described above. Septic mice typically required a lower concentration of isoflurane compared with sham; thus adjustment was made on the basis of the overall appearance and responsiveness of mice during the surgical preparation, but all data were collected at a standardized inhaled isoflurane concentration of 1.5%. A temperature probe (YSI 400, Level 1, Rockland, MA) was inserted into the rectum for initial temperature measurement by a digital thermometer (TM 2000D, RSP, Irvine, CA) as soon as mice were anesthetized. Mice were then placed on the procedure bench with heating pads (T/Pump, 2000D, RSP, Irvine, CA) as soon as mice were anesthetized. Mice were then placed on the procedure bench with heating pads (T/Pump, Gaymar, Orchard Park, NY) and lamps to maintain the body temperature between 36 and 37.5°C. The surgical procedure was performed under an operating microscope (Olympus SZ40, Leeds Instruments, Irving, TX). A small incision was made in the anterior neck to expose the trachea and the left carotid artery. The trachea was incised and intubated with an endotracheal tube modified from a 20-gauge intravenous catheter. The animal was then placed on positive-pressure ventilation using a rodent ventilator (model 683, Harvard, South Natick, MA) with a tidal volume of 400–450 μl and rate of 80–95 breaths per minute. These values were adjusted on the basis of the animal’s carbon dioxide production guided by expired gas capnometry (Capnomac Ultima, Tewksbury, MA). The left carotid artery was exposed and cannulated with stretched PE-10 tubing and transduced to an analog pressure module (MP-100, Biopac Systems, Goleta, CA). The analog signal of the mean arterial pressure was interfaced with the data-acquisition system described below.

A clamshell incision was made over the anterior chest wall 2 mm above the level of the xyphoid process. The chest cavity was entered with small mosquito clamps that were then applied across the sternum. The sternum was transected with an electrocautery system (Valleylab, Force 2, Boulder, CO) and the mediastinum was exposed. A 4-0 silk tie was passed around the inferior vena cava (IVC) just above the diaphragm. The pericardium was excised at the left ventricular apex. The apex was then punctured with a 27½-gauge needle occluded with bone wax. A 1.4-Fr catheter with pressure and conductance sensors (SPR 839, Millar Instruments, Houston, TX) was passed through the puncture along the longitudinal axis of the left ventricle. Left ventricular volume was estimated by the impedance-conductance technique. The catheter’s angle and position were adjusted to obtain optimized flow-volume curves. Specifically, measurements were made at the position from which the maximum volume measurement was obtained.

The conductance catheter was interfaced with a pressure-volume analog signal amplifier (Aria 1, Millar Instruments). Real-time conductance and mean arterial pressure data were collected with an analog-to-digital converter (Power Lab 4SP, ADInstruments, Castle Hill, Australia). All variables were displayed and recorded (Chart ver. 4.12, ADInstruments). Initial pressure-volume curves were assessed. To standardize the preload, 50–100 μl of normal saline were slowly given via the arterial line to reach a left ventricular end-diastolic volume (LVEDV) between 15 and 18 relative volume units (RVU), which corresponded to 40–50 μl. The arbitrary RVU number was converted to true volume by using calibration wells with known diameters of 2–6 mm (Millar Instruments) containing heparinized blood from mice of each group heated to 37°C. Volume measurements were performed with blood from three mice in each experimental group. No significant differences in RVU measurements were observed between groups at any of the well diameters. These determinations were made to ensure that differences in blood resistivity did not exist between groups. The target range of the LVEDV of 40–50 μl was chosen as the end point of resuscitation and was used as the standardized condition for hemodynamic measurements because it was found to be typical of healthy animals undergoing the same procedure with minimal or no blood loss in our pilot experiments.

Left ventricular pressure and volume were measured first at the steady state without IVC occlusion. Heart rate, stroke volume, and cardiac output, as well as pressure development during isovolumic contraction (dp/dtmax) and relaxation (dp/dtmin), were also obtained. After the steady-state measurements were performed, IVC occlusion was performed by gently lifting the tie around the IVC while briefly suspending mechanical ventilation. Left ventricular end-systolic pressure-volume relationship (ESPVR) was obtained for each individual animal at the varying preload status produced by IVC occlusion. Time-varying maximum elastance (Emax) was obtained from the series of pressure-volume relationship regression curves at various preloads. Likewise, preload-recruitable stroke work (PRSW) data were generated with the varying LVEDVs. The slopes of the curves for all animals in the group were numerically averaged. To eliminate parallel conductance and resultant contribution of volume from the myocardium, a calibration with 10 μl of 15% hypertonic saline was conducted as described by Yang et al. (25).

RNAse protection assay. Hearts were harvested and flash frozen in liquid nitrogen. Samples were stored at −80°C until used. Total RNA was isolated using Tri-Reagent (Molecular Research Center, Cincinnati, OH). The RNAse protection assay was performed using the Riboquant system (B-D Pharmingen) per the manufacturer’s instructions. Briefly, radiolabeled RNA probes were synthesized from DNA template sets by using T7 RNA polymerase, [32P]UTP, and pooled control cDNA. Hybridized RNA was then digested with the purified riboprobes and subjected to RNAse digestion. Protected RNA species were separated on 5% polyacrylamide-sequencing gels by use of 0.5× Tris-borate-EDTA running buffer. Gels were run at 50-W constant power for 70 min and dried under vacuum, and the protected fragments were visualized by use of autoradiography.

Assessment of hepatic, renal, and pulmonary injury. Lung injury was determined by measuring wet-to-dry weight and PO2-to-inspired oxygen fraction (FiO2) ratios. Wet-to-dry weight ratios were determined by harvesting lung tissue from euthanized mice. All extraneous tissue was removed; lungs were blotted dry and weighed. Lungs were then desiccated by heating (55°C) in a drying oven for 5 days and weighed. The wet-to-dry weight ratio was calculated as an index of increased lung water. PO2-to-FiO2 ratios were calculated from arterial PO2 measurements obtained from mice breathing 100% oxygen. Blood was harvested by use of heparinized syringes, and blood gas measurements were performed using iStat cartridges (iStat, East Windsor, NJ). Plasma alanine aminotransferase (ALT)/aspartate ami-
notransferase (AST) and blood urea nitrogen (BUN)/creatinine levels were measured as indexes of acute liver and renal injuries, respectively. Blood was obtained by carotid artery laceration. ALT, AST, BUN, and creatinine levels were measured in the clinical chemistry laboratory at the Shriners Burns Hospital, Galveston.

Statistics. Data are expressed as means ± SE. Calculation of dp/dt\textsubscript{max}, dp/dt\textsubscript{min}, E\textsubscript{max}, ESPVR, and PRSW were performed by use of pressure-volume analysis software (PVAN version 3.1, Millar Instruments). Comparisons among groups were performed by one-way analysis of variance followed by a post hoc Tukey’s or Dunnett’s test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Hemodynamic response of CD8KO/αAsGM1 mice after CLP. Hemodynamic measurements were made after placement of the left ventricular conductance catheter and resuscitation of mice to LVEDVs of 40–50 μl (Fig. 1). Wild-type mice had significantly lower mean arterial pressure despite adequate fluid resuscitation compared with sham mice at 18 h after CLP. Mean arterial blood pressure was not significantly different between CD8KO/αAsGM1 and sham mice and was significantly higher in CD8KO/αAsGM1 mice compared with wild-type mice (Fig. 1). Heart rate and stroke volume were not significantly different between sham mice and wild-type or CD8KO/αAsGM1 mice (Fig. 1). Cardiac output was significantly decreased in wild-type mice at 18 h after CLP compared with sham mice but was not significantly different than CD8KO/αAsGM1 mice. Systemic vascular resistance was significantly decreased in wild-type mice compared with sham and CD8KO/αAsGM1 mice (Fig. 1). CD8KO/αAsGM1 mice did not exhibit a significant change in systemic vascular resistance after CLP compared with sham mice.

Cardiac contractile function in CD8KO/αAsGM1 mice after CLP. Cardiac contractile function was determined in sham and post-CLP mice both during the steady state and after transient occlusion of the IVC. Assessment of pressure development over time during contraction and relaxation (dp/dt\textsubscript{max} and dp/dt\textsubscript{min}) of the left ventricle was initially measured during the steady state (Fig. 2). Wild-type mice showed significant decreases in dp/dt\textsubscript{max} and dp/dt\textsubscript{min} at 18 h after CLP compared with sham mice (Fig. 2). Comparison of sham and CD8KO/αAsGM1 mice after CLP did not reveal significant differences in dp/dt\textsubscript{max} and dp/dt\textsubscript{min}, but these parameters were signifi-
significantly improved in CD8KO/αAsGM1 mice compared with wild-type mice at 18 h after CLP. Because dp/dt max is a relatively preload-sensitive marker of contractility, dp/dt max was corrected for LVEDV (Fig. 2). Both wild-type and CD8KO/αAsGM1 mice exhibited significant decreases in (dp/dt max/LVEDV) at 18 h after CLP compared with sham mice. However, dp/dt max/LVEDV determinations were significantly higher in CD8KO/αAsGM1 mice compared with wild-type mice (Fig. 2).

Load-insensitive indicators of left ventricular contractility such as the ESPVR, Emax, and PRSW were determined by measuring the left ventricular pressure-volume relationship during transient IVC occlusion (Fig. 3). ESPVR and Emax were significantly lower in wild-type and CD8KO/αAsGM1 mice after CLP compared with the sham group (Fig. 3). CD8KO/αAsGM1 mice exhibited a significantly higher ESPVR and Emax at 18 h after CLP compared with wild-type mice. PRSW was significantly lower in wild-type mice after CLP compared with sham controls (Fig. 3). PRSW in CD8KO/αAsGM1 mice was not significantly different compared with sham mice but was significantly higher than wild-type mice after CLP (Fig. 3).

Cardiac proinflammatory cytokine expression in CD8KO/αAsGM1 mice after CLP. Proinflammatory cytokines have been shown to cause myocardial dysfunction in models of trauma and systemic injury. In these studies, expression of mRNAs for several proinflammatory cytokines and chemokines were measured in wild-type and CD8KO/αAsGM1 mice at 18 h after CLP (Fig. 4). Heart tissue from wild-type mice expressed mRNAs for the proinflammatory cytokines IL-1α, IL-1β, IL-6, and TNF-α. In addition, expression of MIP-2 mRNA, the mouse homolog of the human chemokine IL-8, was observed in the hearts of wild-type mice at 18 h after CLP. Expression of all of these cytokines and chemokines was markedly decreased in the hearts of CD8KO/αAsGM1 mice compared with wild-type mice (Fig. 4).
Acid-base balance and organ injury in wild-type and CD8KO/αAsGM1 mice after CLP. Metabolic acidosis is a common ramification of tissue hypoperfusion and shock. Because of the altered hemodynamics observed in mice after CLP, studies were undertaken to assess acid-base balance in mice at 18 h after CLP (Fig. 5). Wild-type mice exhibited significant acidosis that was associated with decreased blood bicarbonate levels and increased base deficit. These parameters were not significantly altered in CD8KO/αAsGM1 mice compared with sham mice and were significantly improved in CD8KO/αAsGM1 mice compared with wild-type mice after CLP (Fig. 5). Plasma PCO2 concentrations were not significantly different between groups.

Indexes of specific organ injury were also assessed in mice at 18 h after CLP (Fig. 6). The plasma creatinine concentration was less than 0.1 mg/dl in sham and CD8KO/αAsGM1 mice but was significantly increased in wild-type mice. BUN, AST, and ALT levels were increased in both wild-type and CD8KO/αAsGM1 mice after CLP compared with sham controls but comparison of wild-type and CD8KO/αAsGM1 mice did not show significant differences (Fig. 6). Lung wet-to-dry weight and PO2-to-FIO2 ratios were not significantly different between groups (Fig. 6).

DISCUSSION

The present study shows that CD8KO/αAsGM1 mice have less hemodynamic dysfunction compared with wild-type mice after CLP. Specifically, CD8KO/αAsGM1 mice exhibit less myocardial depression, higher systemic vascular resistance, preserved cardiac output, and sustained systemic arterial blood pressure compared with wild-type controls. The hemodynamic alterations observed in wild-type mice after CLP parallel those described in our laboratory’s previous reports (22, 23) except that cardiac output was decreased in this study. One explanation for this finding is that wild-type mice may be at the
transition from a hyperdynamic state to a state of cardiovascular depression at the 18-h time point. Numerous investigators have shown that a hyperdynamic state will develop during the early stages of sepsis in subjects that have been adequately resuscitated (1, 5). However, subjects in the late stages of septic shock often exhibit myocardial depression with concomitant deterioration of cardiac output and systemic perfusion (4). Our studies were performed at 18 h after CLP. At this time point, wild-type mice exhibit severe hypoactivity, cachexia, and shivering. Mortality occurs at 24–30 h after CLP in this model (18). Therefore, it is likely that the mice utilized in the present study were entering a state of hypodynamic shock. In support of this hypothesis, we previously showed a downward trend in stroke volume and cardiac output from 12 to 18 h after CLP (22). This is in agreement with other studies that have demonstrated a hyperdynamic state during the first 12 h after CLP but development of cardiovascular depression by 20 h post-CLP (12, 26). Another possible explanation for the lower cardiac output is that mice in this study were not adequately resuscitated. This is unlikely because all mice were resuscitated to LVEDVs of 40–50 μl before initiation of cardiovascular measurements. Resuscitation protocols used in this study were identical to those used in our previous studies.

Systemic perfusion appears to be maintained in CD8KO/αAsGM1 mice, as indicated by the absence of metabolic acidosis. Wild-type mice had severe metabolic acidosis by 18 h after CLP. Several studies have shown metabolic acidosis and elevated base deficit to be good surrogate markers of global tissue hypoperfusion (3, 27). The presence of metabolic acidosis indicates the existence of tissue ischemia and anaerobic metabolism. This may be due to local cecal ischemia after the ligation procedure or systemic hypoperfusion secondary to CLP-induced hypotension and decreased cardiac output. The former explanation seems unlikely because CD8KO/αAsGM1 mice underwent the same cecal ligation procedure as wild-type mice but did not exhibit metabolic acidosis. Examination of ceca at 18 h after CLP in both groups showed identical levels of necrosis distal to the ligature. Our observation of increased serum creatinine concentration in wild-type, but not CD8KO/αAsGM1 mice provides further evidence of CLP-induced hypoperfusion and is likely an early sign of renal insufficiency. We were unable to identify differences in indexes of dysfunction of liver or lung when comparing wild-type and CD8KO/αAsGM1 mice in our model. Specifically, plasma ALT and AST concentrations were elevated in both wild-type and CD8KO/αAsGM1 mice after CLP. BUN was also increased in both groups. These findings likely represent the intra-abdominal response to acute gastrointestinal injury. CLP did not cause alterations in lung wet-to-dry weight or PO2-to-FIO2 ratios. Therefore, CLP appears to induce a state of cardiovascular instability and shock without evidence of specific injury to liver and lung in wild-type mice, whereas CD8KO/αAsGM1 mice are resistant to these alterations.
CD8KO/αAsGM1 mice clearly exhibit an attenuated proinflammatory response after CLP. Our laboratory previously reported that CD8KO/αAsGM1 mice have much lower levels of proinflammatory cytokines in peritoneal fluid and blood after CLP compared with wild-type mice (18). The present study extends this observation by showing increased expression of mRNAs for several proinflammatory cytokines and chemokines in the hearts of wild-type but not CD8KO/αAsGM1 mice. The heart has been shown to be a particularly rich source of proinflammatory cytokines during systemic inflammation caused by sepsis, burns, and trauma (6). Proinflammatory cytokines are produced by cardiac myocytes in response to circulating mediators present in serum from burned subjects as well as to bacterial products such as endotoxin (7, 10, 13). Proinflammatory cytokines directly contribute to myocardial depression during systemic inflammation caused by trauma or sepsis (4, 10, 13, 14, 21). The functional roles of TNF-α, IL-1β, and IL-6 in causing myocardial dysfunction after burn injuries have been extensively described by Horton and colleagues (6, 7). However, it is unclear what relative impact circulating cytokines have compared with those produced locally by cardiac myocytes. Our study does not demonstrate a direct cause-and-effect relationship between elevated myocardial cytokine levels and left ventricular dysfunction. However, a strong correlation is demonstrated, and on the basis of the functional studies of previous investigators, it is likely that the elevated systemic and intracardiac cytokine levels observed in wild-type mice after CLP contribute to the observed myocardial depression. Nevertheless, other factors such as macrophage inhibitory factor, oxygen free radicals, and nitric oxide have also been implicated in inflammation-induced myocardial dysfunction and may play a role in our model (6). Furthermore, it is also possible that the worsening metabolic acidosis seen in wild-type mice contributes to the cardiovascular collapse observed in the post-CLP period. The association between systemic acidosis and cardiovascular dysfunction during sepsis has been recognized (9). In fact, some investigators have shown that metabolic acidosis potentiates the production of proinflammatory cytokines (8). Therefore, the coexistence of metabolic acidosis and systemic inflammation may serve as potentiating factors for cardiovascular dysfunction during sepsis.

Understanding of the mechanisms by which CD8+ T and NK cell depletion confers protection from CLP-induced injury is complicated by the complexity of the CLP model. It is likely that CLP causes both acute infection and gut ischemia. The high bacterial counts in blood, peritoneal fluid, and lung after CLP demonstrate the presence of bacterial dissemination and systemic infection (18). Intestinal ischemia is also likely to contribute significantly to CLP-induced morbidity. However, the ischemic component of CLP has not been widely studied. The blood supply to the rodent cecum arises primarily from the superior mesenteric artery and runs from the base to the distal tip of cecum (11). Therefore, ligation of the cecum at its base will disrupt blood flow to areas distal to the ligation site resulting in tissue ischemia. The functional importance of cecal ischemia in CLP-induced injury is supported by the studies of Singleton and Wischmeyer (20), in which the length of cecum ligated, rather than puncture size, was the major predictor of inflammation and mortality. Other studies have shown that resection of the ischemic cecum will reverse CLP-induced mortality (16). Nevertheless, the functional role of CD8+ T and NK cells in mediating ischemia-induced injury in this model needs to be fully examined.

In conclusion, mortality of wild-type mice after acutely lethal CLP is likely due to cardiovascular collapse and shock. These cardiovascular abnormalities are attenuated in CD8KO/αAsGM1 mice and are associated with diminished intracardiac and systemic inflammation. The underlying mechanisms responsible for these observations remain to be fully defined. However, it is likely that depletion of NK and CD8+ T cells causes attenuation of the CLP-induced proinflammatory response, resulting in preserved hemodynamics and cardiac contractile function with resultant resistance to mortality after CLP.

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