isolated neutrophils was similar between Ido$^{+/+}$ and Ido$^{-/-}$ mice analyzed by a bactericidal-capacity assay (data not shown). These results suggest that the increase in recruited peritoneal-cavity circulating neutrophils and mononuclear cells may be involved in containment of the infection to the local focus and that Ido has an inhibitory effect on the recruitment of neutrophils and mononuclear cells, resulting in progression to sepsis.

CLP increased Ido mRNA expression in CD11b^{+} peritoneal cells. We hypothesized that the Ido induced by CLP in peritoneal cells inhibits its recruitment because inhibition of Ido increased the recruitment of neutrophils and mononuclear cells to the peritoneal cavity after surgery. Indeed, expression of Ido mRNA was significantly increased in peritoneal cells isolated from Ido$^{+/+}$ mice by CLP (Fig. 4A). Furthermore, Ido mRNA was expressed in the CD11b^{+} and CD11c^{+} cells isolated from the peritoneal cells after CLP (Fig. 4B). Specifically, most Ido^{+} peritoneal cells showed double staining for CD11b (Fig. 4C), suggesting that L-Kyn is mainly produced by CD11b^{+} cells among the other peritoneal cells. The number of CD11b^{+} cells in the peritoneal cavity was increased 6 h after CLP, and CD11b^{+} cells were induced to a greater extent by CLP in Ido$^{-/-}$ mice than in Ido$^{+/+}$ mice (Fig. 4D). To examine how CLP increases Ido in peritoneal cells, the cultured peritoneal cells from mice were treated with LPS. LPS treatment increased Ido mRNA expression in the cultured peritoneal cells isolated from Ido$^{+/+}$ mice (Fig. 4E). These results suggest that bacterial LPS induced by CLP increases Ido expression in the peritoneal CD11b^{+} cells and that increase of Ido activation may inhibit the recruitment of neutrophils and mononuclear cells to the infection focus.

Ido deficiency in BM-derived cells with delayed mortality from CLP. As described above, Ido in the peritoneal CD11b^{+} cells may be involved in increasing mortality rates after CLP. To explore the involvement of Ido in the BM-derived cells, we generated Ido chimeric mice by using a combination of irradiation and BMT. The Ido$^{-/-}$ BM-transplanted Ido$^{+/+}$ mice (donor cells, Ido$^{-/-}$ BM cells; recipient animals, Ido$^{+/+}$ mice) or Ido$^{-/-}$ mice (donor cells, Ido$^{-/-}$ BM cells; recipient animals, Ido$^{-/-}$ mice) showed higher survival rates following CLP than did the Ido$^{+/+}$ BM-transplanted Ido$^{+/+}$ mice (donor cells, Ido$^{+/+}$ BM cells; recipient animals, Ido$^{+/+}$ mice) or Ido$^{-/-}$ mice (donor cells, Ido$^{+/+}$ BM cells; recipient animals, Ido$^{-/-}$ mice) (Fig. 5A). Serum L-Kyn levels significantly increased 6 h after CLP in Ido$^{+/+}$ BM-transplanted Ido$^{+/+}$ mice and Ido$^{-/-}$ mice, whereas CLP did not affect L-Kyn levels in the Ido$^{-/-}$ BM-transplanted Ido$^{+/+}$ mice or Ido$^{-/-}$ mice (Fig. 5B). Thus, Ido in BM-derived cells, which include CD11b^{+} cells, is involved in the progression to sepsis after CLP.

Ido is involved in chemokine production at the infection focus. To examine how Ido regulates recruitment of neutrophils and mononuclear cells to the site of infection, we measured the levels of chemotactic chemokines in Ido$^{+/+}$ and Ido$^{-/-}$ mice after CLP. Expression levels of CXCL-2 and CXCL-1 mRNA in the peritoneal cells from Ido$^{-/-}$ mice were significantly higher than those from Ido$^{+/+}$ mice 6 h after CLP (Fig. 6A), and the expression level of IL-17 mRNA in peritoneal cells from Ido$^{-/-}$ mice tended to increase compared to that from Ido$^{+/+}$ mice. Similarly, serum CXCL-2 levels after CLP in Ido$^{-/-}$ mice were also higher than those in Ido$^{+/+}$ mice (Fig. 6B). Moreover, the increase of CXCL-2 in Ido$^{-/-}$ mice after CLP was prevented by pretreatment with L-Kyn (Fig. 6B). In addition, LPS administration to the isolated

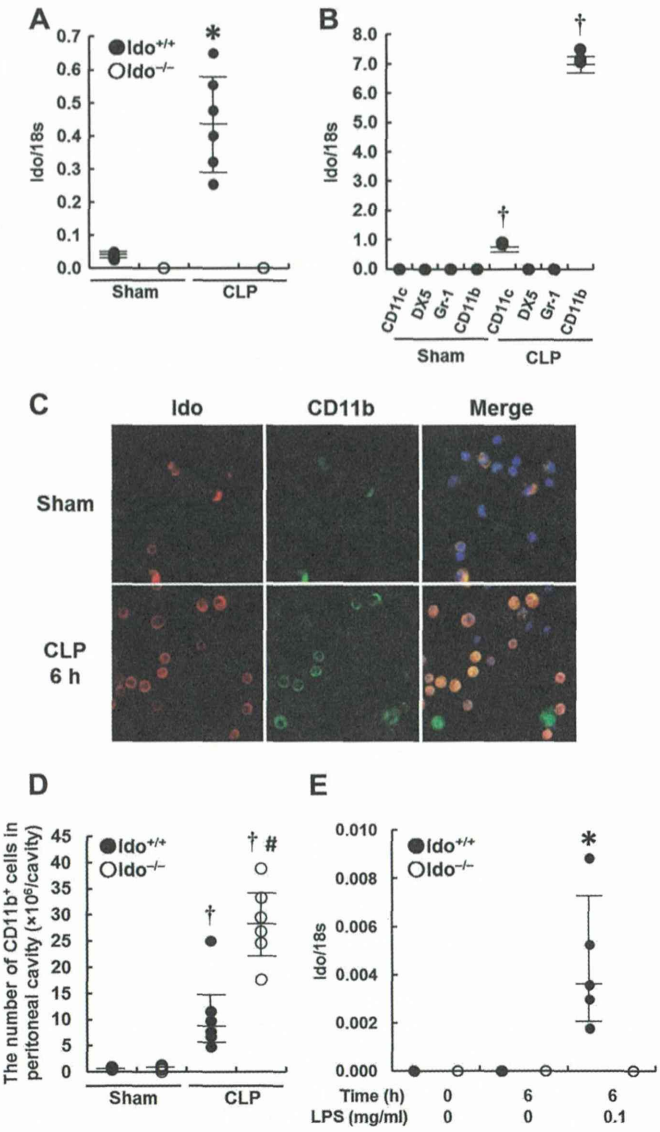

FIG 4 Ido mRNA was increased in peritoneal cells by CLP. Ido$^{+/+}$ and Ido$^{-/-}$ mice underwent CLP. The animals were humanly killed at the indicated times. (A) mRNA expression levels of Ido in peritoneal cells isolated from sham- or CLP-operated mice at 6 h after surgery were determined by quantitative real-time RT-PCR. (B) Cell fractionation was performed with the indicated antibodies and MACS magnetic beads from peritoneal cells isolated from sham- or CLP-operated mice 6 h after surgery. (C and D) Peritoneal cells were isolated from sham- or CLP-operated mice 6 h after surgery. Expression of CD11b (green), Ido (red), and DAPI nuclei (blue) in peritoneal cells was examined by immunofluorescent staining. The merged images are shown on the right. The CD11b^{+} cells were counted. (E) Peritoneal cells isolated from Ido$^{+/+}$ or Ido$^{-/-}$ mice were treated or not with LPS (0.1 μg/ml) for 6 h, and mRNA expression levels of Ido were determined. The data are median IQR values from at least 5 independent experiments, with error bars indicating the range. *, $P < 0.01$ compared with Ido$^{-/-}$ mice; #, $P < 0.05$ compared with Ido$^{+/+}$ CLP-operated mice; and †, $P < 0.001$ compared with sham-operated mice using ANOVA.

cultured peritoneal cells increased CXCL-2 and CXCL-1 mRNA, and the increase was greater in cultured Ido$^{-/-}$ peritoneal cells than in Ido$^{+/+}$ cells (Fig. 6C), suggesting that Ido induction by LPS has inhibitory effects against chemokine production by LPS in peritoneal cells. In addition to increased chemokine production

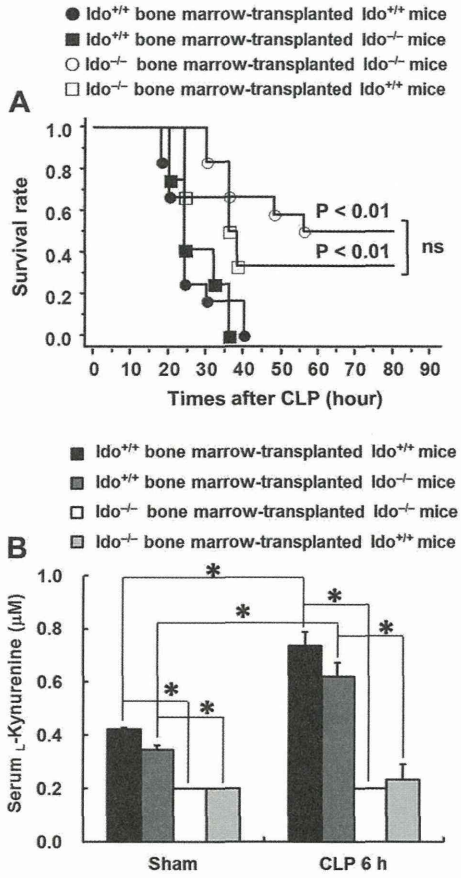

FIG 5 Ido of bone marrow-derived cells is involved in mortality after CLP. $Ido^{+/+}$ or $Ido^{-/-}$ bone marrow cells (5×10^6) were injected into lethally irradiated $Ido^{+/+}$ or $Ido^{-/-}$ recipient mice. The chimeric mice were subjected to CLP 4 weeks after BMT. (A) Survival curves of animals after CLP. Statistically significant differences between the groups were determined using a log-rank test. The *P* values compared with $Ido^{+/+}$ donor mice are shown. (B) The animals were humanely killed 6 h after surgery, and serum L-Kyn levels were measured. The data are means and SD from at least 5 independent experiments. *, $P < 0.05$ using ANOVA; ns, not significant.

by LPS in peritoneal cells, the number of $CD11b^+$ cells in peritoneal cells was higher in $Ido^{-/-}$ mice, as described above (Fig. 4E). These findings suggest that Ido inhibits chemokine production in peritoneal cells due to synergistic effects of reduced productivity and cell numbers in its source. Indeed, LPS-induced CXCL-2 and CXCL-1 production and secretion into the medium were higher in peritoneal cells isolated from $Ido^{-/-}$ mice after CLP than in those from $Ido^{+/+}$ mice (Fig. 6D). These results suggest that reduction of chemokine production in peritoneal $CD11b^+$ cells occurs due to L-Kyn production by Ido induction after CLP and that it may reduce the recruitment of neutrophils and mononuclear cells to the peritoneal cavity.

DISCUSSION

The present study investigated the contribution of Ido to the progression of sepsis due to CLP-induced bacterial peritonitis. The results indicate that Ido increases mortality rates through reduction of recruited neutrophils and mononuclear cells into the infection focus.

It has been reported that Ido plays a pivotal role in immune tolerance and that Ido is expressed in various types of cells, including astrocytes (17), epithelial and endothelial cells (18), tumor cells (19, 20), DCs (16), and macrophages (21, 22, 38). In CLP-induced bacterial peritonitis, Ido expression was increased in $CD11b^+$ peritoneal cells, but not in neutrophils or NK cells, whereas its inhibition reduced mortality. LPS increased Ido expression in peritoneal cells *in vitro*, and Ido^+ BM-derived cells were involved in increasing mortality rates. Thus, Ido expression in $CD11b^+$ peritoneal cells has important roles in immune regulation in this model. Various functions of Ido for immune regulation have been reported. Activation of Ido in DCs suppresses T cell responses (39) and induces the generation of regulatory T cells (Tregs) via Trp metabolites in experimental autoimmune encephalomyelitis (40). Ido inhibits IL-17 production and promotes cytotoxic potential in mucosal NK cells during SIV infection (41). IFN-γ-induced Ido is involved in the suppression of Th17 in CIA, and the suppression of Th17 by IFN-γ was abolished with 1-MT (42). Furthermore, inhibition of Ido enhances T-cell response to influenza virus infection (43) and increases IL-10 production in BM-derived DCs (44).

In this study, we found that Ido decreased the number of $CD11b^+$ peritoneal cells and the productivity of CXCL-2 and CXCL-1 in peritoneal cells. Chemokine production by LPS is regulated by NF-κB signaling (45, 46), and L-Kyn metabolites inhibit NF-κB activation by specifically targeting phosphoinositide-dependent protein kinase 1 (47). Thus, LPS stimulates both NF-κB and Ido, and the produced L-Kyn inhibits NF-κB, resulting in the reduction of CXCL-2 and CXCL-1 production. Indeed, pretreatment with L-Kyn prevented the increase of CXCL-2 and CXCL-1 production in $Ido^{-/-}$ mice. Moreover, pretreatment with L-Kyn reversed the mortality of $Ido^{-/-}$ mice. It is known that the downstream metabolites of Trp, including L-Kyn, suppress immune reactivity (28, 29). L-Kyn also functions as an endogenous ligand for the aryl hydrocarbon receptor, which modulates the functions of immune cells (48). In addition to the increased metabolites from Trp, Ido activation induces breakdown of Trp, which suppresses immune cell proliferation by reducing the availability of this essential amino acid under local tissue microenvironments (49). Although Ido depletion could explain the increase of $CD11b^+$ cell recruitment in the peritoneal cavity via cell proliferation, the precise underlying mechanisms remain unclear, and further studies are needed to clarify these mechanisms.

It has been reported that Ido potentially has a dual role. Pathogens may reduce their growth by Ido-mediated tryptophan degradation (50). On the other hand, it may modulate immune cell recruitment and function and thus be detrimental to the host (32). Although Ido has both beneficial and disadvantageous effects in various cells, disadvantageous effects of Ido have been reported in immune cells (19–22, 51, 52). In this study, blockage of Ido in $CD11b^+$ peritoneal cells reduced mortality after CLP, as well as increasing the rate of neutrophil and mononuclear cell recruitment into the infection focus. Similarly, another study found that 1-MT administration improves the survival rates of mice with sepsis induced by injection of cecal content (44).

As local infection progresses to sepsis, Ido shows further disadvantageous effects, including impaired endothelial function, decreased endothelial nitric oxide, and impaired immune functions (53). Recent studies have described Ido activity in the plasma as a prognostic factor in bacteremic patients and as a risk factor for posttraumatic sepsis (54, 55). There are many other pathways that

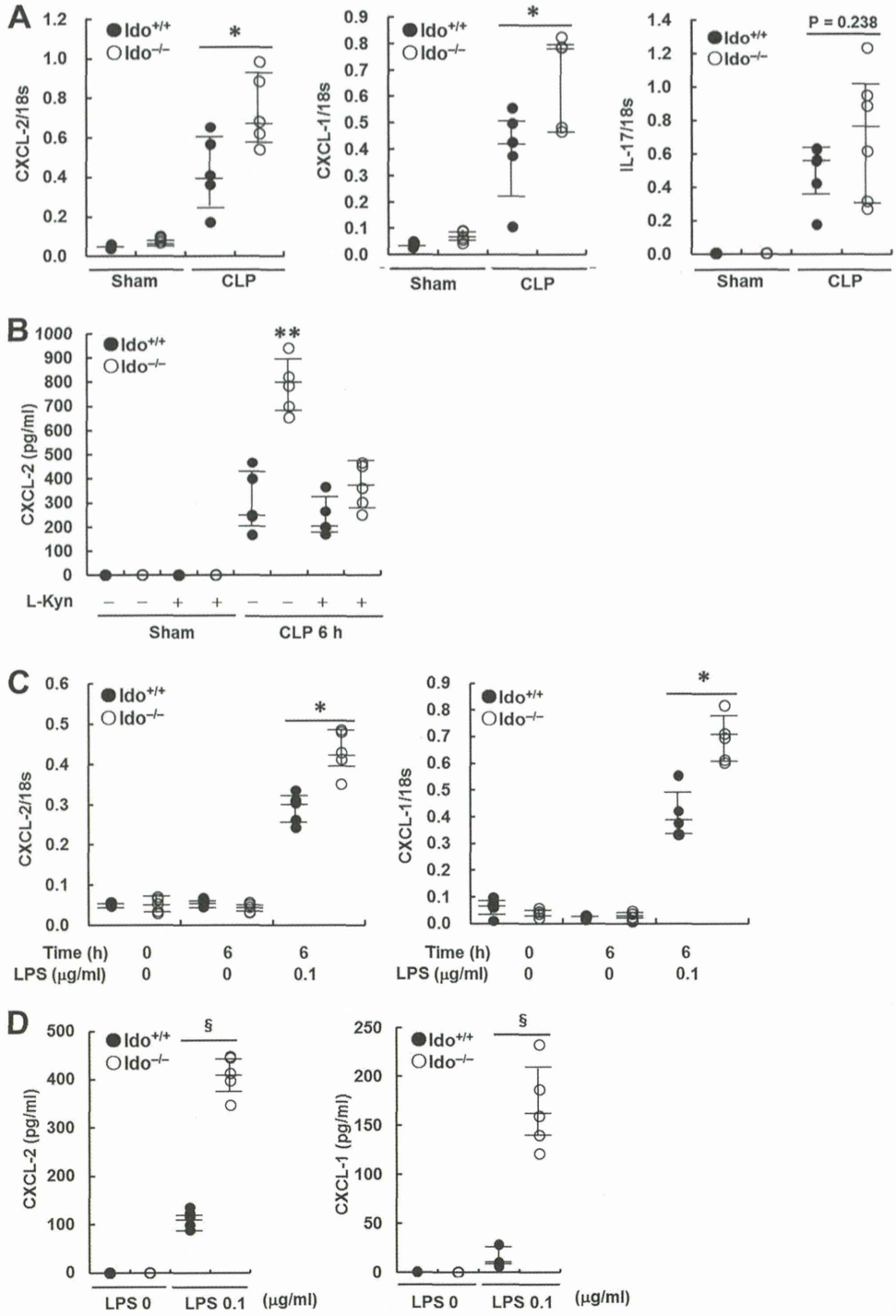

FIG 6 Deficiency of Ido increased chemokines after CLP. (A to C) $Ido^{+/+}$ and $Ido^{-/-}$ mice were subjected to CLP. The animals were humanly killed 6 h after surgery. (A) mRNA expression levels of CXCL-2, CXCL-1, and IL-17 in the isolated peritoneal cells were determined by quantitative real-time RT-PCR. (B) Serum CXCL-2 levels in the $Ido^{+/+}$ or $Ido^{-/-}$ mice or L-Kyn-treated $Ido^{+/+}$ or $Ido^{-/-}$ mice 6 h after surgery were quantified using ELISA. (C) Peritoneal cells were isolated from nontreated $Ido^{+/+}$ or $Ido^{-/-}$ mice. The isolated cells were cultured for 2 h and were then treated or not with LPS (0.1 μg/ml) for the indicated periods of time. mRNA expression levels of CXCL-2 and CXCL-1 were determined by quantitative real-time RT-PCR. (D) Peritoneal cells were isolated from $Ido^{+/+}$ or $Ido^{-/-}$ mice operated on with CLP 6 h after surgery. The isolated cells were cultured for 2 h and were then treated or not with LPS (0.1 μg/ml) for 6 h, and the CXCL-2 and CXCL-1 concentrations in the culture medium were measured by ELISA. The data are expressed as the median IQR from 6 independent experiments. *, $P < 0.05$ compared with $Ido^{+/+}$ CLP mice; **, $P < 0.01$ compared with $Ido^{+/+}$ mice or L-Kyn-treated $Ido^{-/-}$ mice; §, $P < 0.01$ compared with $Ido^{-/-}$ peritoneal cells, using ANOVA.

produce leukocyte trafficking into the local focus. For example, granulocyte colony-stimulating factor (G-CSF) is known to cause extreme leukocytosis. A case of G-CSF-producing lung cancer with marked leukocytosis rapidly led to severe acute respiratory distress syndrome after pneumonia developed (56). Thus, inhibition of Ido may improve immune response to bacterial infection from the local infection focus to a systemic inflammatory response and may be more useful than other immunomodulatory strategies.

The experiment was restricted to a lethal model of CLP. It is therefore uncertain that Ido function would be the same in a subleathal model or with antibiotic therapy. Moreover, it is possible that the mechanism by which Ido functions in an intravenous-infection model is very different from the CLP model. Further studies are needed to resolve these uncertainties. In conclusion, we observed that Ido activation in peritoneal CD11b$^+$ cells aggravated peritonitis and sepsis. Thus, blockade of Ido plays a critical role in host protection during bacterial peritonitis and sepsis.

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