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Poly(ferulic acid) nanocarrier enhances chemotherapy sensitivity of acute myeloid leukemia by selectively targeting inflammatory macrophages

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ABSTRACT

Macrophages, as a subset of innate immune cells, play a pivotal role in the initiation, maintenance, and resolution of inflammatory responses during tissue damage repair, defense against infections, and tumor progression. However, the mechanisms by which macrophages regulate inflammation in acute myeloid leukemia (AML) and their involvement in the chemotherapeutic effect remain elusive. In this study, we have identified that AML cells stimulate macrophage expansion by activating the colony-stimulating factor 1 receptor (CSF1R) pathway. The expanded macrophages activate nuclear factor kappa-B (NFκB) to induce the expression of inflammatory factors, thereby maintaining leukemic cell quiescence and promoting cell survival following chemotherapy. Furthermore, we have successfully utilized a poly(ferulic acid) nanocarrier to selectively target macrophages for inhibiting the NFκB-mediated inflammation, ultimately enhancing chemotherapy efficacy against AML. Taken together, our findings highlight the crucial role of macrophage-induced inflammation in conferring chemoresistance to AML, and demonstrate the potential of a targeted nanocarrier specifically designed for inflammatory macrophages to improve the AML chemotherapeutic outcomes.

Acute myeloid leukemia (AML) is a heterogeneous hematopoietic malignancy characterized by a differentiation block of hematopoietic stem/progenitor cells and the accumulation of immature myeloid blasts, leading to eventual bone marrow failure if left untreated [1]. The standard AML treatment regimen over last decades has been the internationally used "7 + 3" induction therapy, which consists of cytarabine (Ara-C) for 7 days and anthracycline such as doxorubicin (DOX) for 3 days [2]. Despite some AML patients initially achieve complete remission after chemotherapy, the rate of 5-year survival remains unsatisfactory, especially in patients over 60 years old, due to chemoresistance and relapse [3–5].

Macrophages are innate immune cells that play a fundamental role in initiating, maintaining and resolving inflammatory responses during pathological processes such as tissue damage repair, anti-infection defense, and tumor progression [6,7]. Inflammatory macrophages not only release cytokines and growth factors to facilitate the tumor cell proliferation and survival, but also suppress the activity of other immune cells involved in antitumor responses, including T cells and natural killer cells [8]. Colony-stimulating factor 1 receptor (CSF1R) is a macrophage-specific cell surface glycoprotein critical for activating inflammatory macrophages [9]. Several clinical trials using CSF1R inhibitors for tumor treatment have yielded limited success, partially due to the unspecific impact of CSF1R inhibitors on macrophage function in normal tissues [6,10].

The cumulative evidence indicates that inflammation enhances AML survival during chemotherapy, resulting in chemoresistance [11–13]. Leukemic blasts or microenvironment, such as macrophages and mesenchymal stromal cells, secrete inflammatory factors [14–16], while intensive chemotherapy further triggers the

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release of pro-inflammatory cytokine in AML patients [17]. Inflammation may be exacerbated by infection during chemotherapy-induced myelosuppression or hyperinflammatory states [18]. For instance, autocrine tumor necrosis factor alpha (TNFα) secretion maintains high nuclear factor kappa-B (NFκB) activity in leukemia blasts in myeloid leukemia mouse models, forming the NFκB/TNFα positive feedback loop. Genetic ablation of TNFα or NFκB significantly inhibits leukemia progression *in vivo* [19]. As AML predominantly affects older individuals, age-induced inflammation may contribute to AML development in elderly patients. In clinical practice, interleukin-1 (IL-1) and IL-6 have been associated with poor prognosis, chemoresistance, and myelosuppression in AML [20–23]. Elevated levels of pro-inflammatory cytokine IL-1 and IL-1 receptors in AML patients promote profound expansion of myeloid progenitors in about 67% of AML patients and suppress normal progenitor growth [20]. In pediatric AML, IL-6-induced signal transducers and activators of transduction-3 (STAT3) signaling frequently intensifies at relapse, correlating with inferior survival after relapse. Moreover, exogenous IL-6 reduced mitoxantrone-induced apoptosis in cultured cells and primary pediatric AML samples *in vitro* [23]. Intriguingly, preliminary data suggest that dexamethasone improves the outcome of AML patients undergoing intensive chemotherapy [24,25]. However, the clinical application of inflammation inhibitors, such as NFκB inhibitor bortezomib, the anti-IL-6 antibody siltuximab, and the IL-1 receptor antagonist, has been unsuccessful due to the non-specificity, severe side effects and futility [13].

Macrophages secrete inflammatory factors in malignant tumors and during viral or bacterial infections [26]. However, the regulation of macrophage inflammation and their role in the chemotherapeutic effect of AML remains unknown. Here in this study, we have identified that macrophages secrete inflammatory factors to inhibit leukemic cell cycle entry, resulting in resistance to chemotherapy. Numerous nanoparticles derived from nucleic acids, peptides, cellular vesicles or small molecules have demonstrated potent therapeutic effect against solid tumors [27–31]. Here, we utilized a poly(ferulic acid) nanocarrier with anti-tumor activity in colon cancer [32] to selectively target macrophages for the purpose of inhibiting inflammation and enhancing the chemotherapy efficacy against AML.

The zebrafish xenograft model has emerged as a valuable tool for studying tumor biology and interactions between tumor and the immune system [33–35]. In our previous work, we have established a leukemia-xenografted zebrafish model by injecting AML cells into two-day post fertilization (2 dpf) zebrafish larvae and observed that leukemia cells colonized in the zebrafish caudal hematopoietic tissue (CHT) were resistant to chemotherapy, indicating a potential role of the hematopoietic microenvironment in promoting chemoresistance [36]. The neutrophils and macrophages are the primary immune cells in 2 dpf zebrafish larvae as adaptive immunity has not yet developed at this stage [37,38]. To evaluate whether the xenografted leukemia cells alter the immune microenvironment, we analyzed the number of neutrophils and macrophages. We injected a panel of cultured leukemia cells labeled with CM-Dil into Tg(*mpeg1.1:GFP-NTR*) and Tg(*lyz:GFP*) zebrafish hosts, which label macrophages and neutrophils, respectively. As early as 24-h post injection (24 hpi), we detected a significant higher number of macrophages in the xenografted group compared to the control group (Figs. 1A–C, $P < 0.01$ for MV4-11, $P < 0.01$ for HL60, $P < 0.0001$ for Kasumi-1). In the meanwhile, we found that the xenografted leukemia cells had no significant impact on the number of neutrophils (Figs. 1D and F).

Since CSF1R signaling is critical to initiate the chemotaxis and expansion of macrophages [39,40], we injected Kasumi-1 cells into *csf1ra*-deficient (*fms*-/-) zebrafish larvae [41]. The results showed that *csf1ra* deficiency significantly decreased the cell number of *mfap4* expressing macrophages, but not *lyz* expressing neutrophils, at 24 hpi (Fig. 1G). Consistently, when we pretreated zebrafish larvae with PLX5622, the selective CSF1R inhibitor, the macrophage expansion was effectively inhibited after Kasumi-1 cell injection (Fig. 1H). These results suggest that the xenografted leukemia cells induced macrophage expansion through activating the CSF1R signaling pathway.

As macrophages are the major mediator of the inflammatory microenvironment, we further examined whether the increased number of macrophages altered the expression of pro-inflammatory and anti-inflammatory factors in leukemia-xenografted zebrafish. The mRNA expression of inflammatory cytokines (including *tnfa*, *il-6*, *il-1b*, *mmp-9*) and anti-inflammatory factors (including *il-4* and *il-10*) were significantly up-regulated from 2 hpi to 6 hpi (Fig. 2A). Then, we injected Kasumi-1 cells into siblings or *fms* mutants, respectively. The results showed that, compared to sibling xenografts, leukemia cells did not induce high expression of inflammatory and anti-inflammatory factors in *fms* mutants (Fig. 2B). The Tg(*mpeg1.1:GFP-NTR*) transgenic line enables the temporally controlled ablation of macrophages by the toxic nitroreductase activated with ronidazole (RNZ) (Fig. 2C) [42]. Ablating macrophages reduced the expression of inflammatory and anti-inflammatory factors caused by leukemia (Fig. 2D), which suggested that macrophages were the main source of inflammatory factors in leukemic xenografts of zebrafish models. In contrast, clearance of neutrophils slightly reduced *mmp-9* and *il-4* expressions, but did not affect the expressions of *tnfa*, *il-6*, *il-1b* (Fig. S1 in Supporting information), suggesting that pro-inflammatory factors were mainly derived from macrophages rather than neutrophils in the zebrafish leukemia xenografts.

NFκB is the transcription factor essential for inflammatory factor production and NFκB activation in macrophages is positively correlated with increased carcinogenesis in various experimental models of inflammation-associated cancer [43]. We further examined whether macrophages activated the expression of inflammatory factors through the NFκB pathway. We treated RAW264.7, the macrophage cell line, with lipopolysaccharides (LPS) and found that the protein level of inhibitor kappa B alpha (IκBα), which blocks NFκB nuclear entry and activation, was decreased and the mRNA levels of *TNF-α*, *IL-6* and *IL-1b* significantly upregulated. Pretreatment with NFκB inhibitor JSH-23 reversed the degradation of IκBα (Fig. 2E) and reduced the mRNA expression of *TNF-α*, *IL-6* and *IL-1b* in LPS-treated RAW264.7 (Fig. 2F). Consistent with this, JSH-23 also decreased the expression of leukemia-induced inflammatory factors induced in zebrafish (Fig. 2G), which suggested that NFκB activation in macrophages contributed to the production of these inflammatory factors.

Dysregulation of complex interactions between pro-inflammatory and anti-inflammatory cytokines may create a pro-tumor inflammatory microenvironment that plays a role in many aspects of AML, including disease progression, chemoresistance and myelosuppression [23,44,45]. Previous studies have shown that high level of inflammatory factors in plasma and bone marrow fluid is poor indicators for AML patient prognosis [22,46,47]. However, whether inflammatory factors are involved in the regulation of AML chemoresistance remains unclear. To determine whether inflammatory factors regulate chemotherapeutic effect of AML, we inhibited the expression of inflammatory factors in zebrafish by ablating macrophages or inhibiting NFκB pathway. As shown in Figs. S2A and B (Supporting information), the xenografted leukemic cells exhibited resistance to the DOX-induced cell death, whereas depletion of macrophages with RNZ treated Tg(*mpeg1.1:GFP-NTR*) transgenic zebrafish enhanced the sensitivity of leukemia cells to DOX. Meanwhile, compared with the sibling group, more leukemia cells were killed by DOX in *fms* mutant group (Figs. S2C and D in Supporting information).

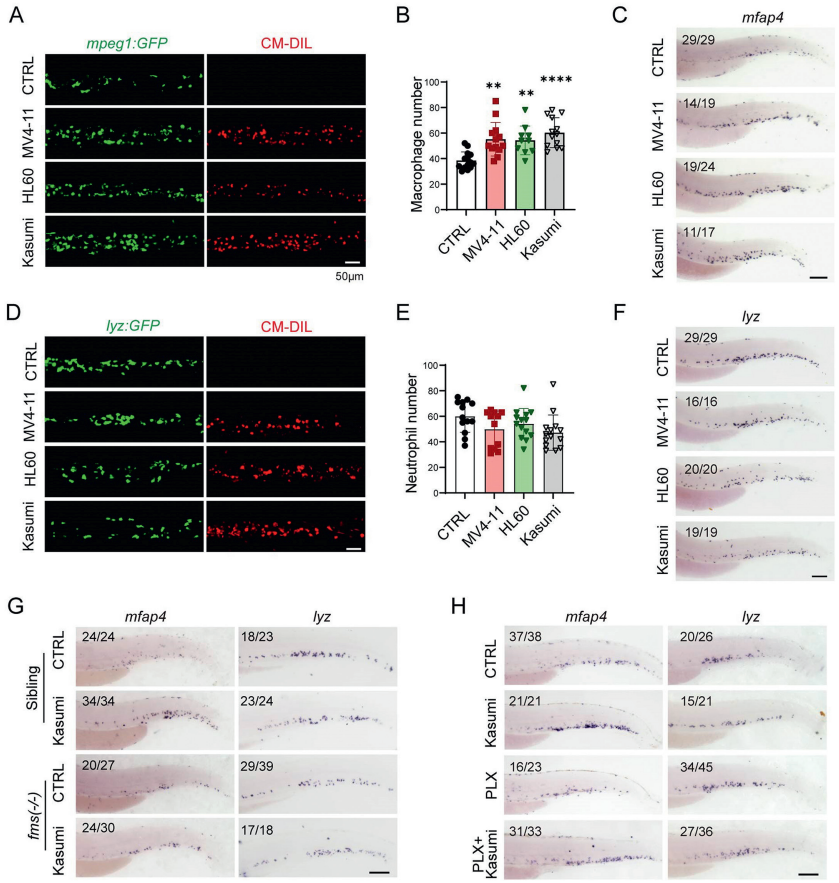

Fig. 1. Xenografted leukemia cells induced macrophage expansion by activating CSF1R. (A, B) The Tg(*mpeg1.1:GFP-NTR*) transgenic zebrafish at 2 dpf were microinjected with PBS or CM-DiI labeled MV4-11, HL60 and Kasumi-1 cells ($n \geq 3$). Represented images of macrophages (green) and leukemia cells (red) in zebrafish CHT and macrophage number were analyzed at 6 hpi. Scale bar: 50 μm. (C) The *mfap4* expression in leukemia-xenografted zebrafish larvae at 6 hpi was analyzed with the whole-mount *in situ* hybridization (WISH). Scale bar: 100 μm. (D, E) PBS or CM-DiI labeled MV4-11, HL60 and Kasumi-1 cells were transplanted into Tg(*lyz:GFP*) transgenic zebrafish ($n \geq 3$). Represented images of neutrophils (green) and leukemia cells (red) in zebrafish CHT and neutrophil number were analyzed at 6 hpi. Scale bar: 50 μm. (F) The *lyz* expression in leukemia-xenografted zebrafish larvae at 6 hpi was analyzed with WISH. Scale bar: 100 μm. (G) Kasumi-1 cells were transplanted into *fms* mutant or siblings. The expression levels of *mfap4* and *lyz* in leukemia-xenografted zebrafish were detected by WISH. Scale bar: 100 μm. (H) The expression levels of *mfap4* and *lyz* in leukemia-xenografted zebrafish pre-treated with PLX5622 were detected by WISH. Scale bar: 100 μm. Data were expressed as mean ± standard deviation (SD). $^{**}P < 0.01$, $^{****}P < 0.0001$.

Similarly, leukemia cells that transplanted into PLX5622-treated zebrafish larvae also demonstrated increased sensitivity to DOX (Figs. S2E and F in Supporting information). We next inhibited NFκB with JSH-23 in host zebrafish larvae before transplanting leukemia cells and administering DOX, and the results showed that JSH-23 pretreatment enhanced the sensitivity of leukemia cells to DOX (Figs. S2G and H in Supporting information). Taken together, our results demonstrated that inhibiting inflammatory factors sensitized leukemia cells to chemotherapy in leukemia-xenografted zebrafish.

Quiescence (G0) is cell cycle-arrested state that render cancer cells distinct properties including the ability to inhibit proliferation, differentiation, apoptosis, and survive unfavorable conditions such as chemotherapy [48–51]. The quiescent leukemia cells in hematological malignancy exhibit reduced sensitivity to chemotherapy drugs that mainly target and rapidly dividing cells [52,53]. To better understand the leukemia drug resistance in the inflammatory environment, we first examined leukemia proliferation with or without macrophage clearance using Tg(*mpeg1.1:GFP-NTR*) transgenic zebrafish. Primary AML cells were obtained from bone marrow biopsy of AML patients at Department of Pediatric Hematology of Sun Yat-sen Memorial Hospital (Table S1 in Supporting information). The use of the clinical specimens was approved by the ethics committee of the Sun Yat-sen Memorial Hospital in accordance with international guidelines and the ethical standards outlined in the Declaration of Helsinki. We transplanted different leukemia cell samples including K562, MV4-11 and primary leukemia cells from an AML patient, and found that macrophage ablation with RNZ increased Ki-67+ leukemia cell (Figs. 3A and B). In the meanwhile, macrophage ablation had no effect on the apoptosis of xenografted leukemia cells in zebrafish (Figs. 3C and D). This suggests that inflammatory factors inhibited leukemia cell proliferation. We next cultured leukemia cells with the supernatant of the LPS-treated RAW264.7, which enriches pro-inflammatory factors, to verify the relationship between inflammation, cell cycle and chemoresistance. The results showed that the RAW264.7 supernatant treated with LPS but not LPS itself blocked leukemia cells to enter S phase (Figs. 3E and F) and maintained them stay in G0 phase (Figs. 3G and H). In concordance with *in vivo* results, LPS-treated RAW264.7 supernatant did not influence leukemia cell apoptosis compared to normal RAW264.7 supernatant (Figs. 3I and J). Furthermore, we found that LPS-treated RAW264.7 supernatant promoted leukemia cell survival in presence of doxorubicin treatment (Fig. 3K), whereas inhibition of inflammation with JSH-23 reversed the inflammation induced leukemia chemoresistance (Fig. 3L). The results above suggested that pro-inflammatory factors inhibited leukemic cell cycle entry and maintained quiescence to induce chemoresistance.

Ferulic acid (FA) is a phenolic acid substance derived from vegetables, fruits, cereals, and some herbs which acts as a potent

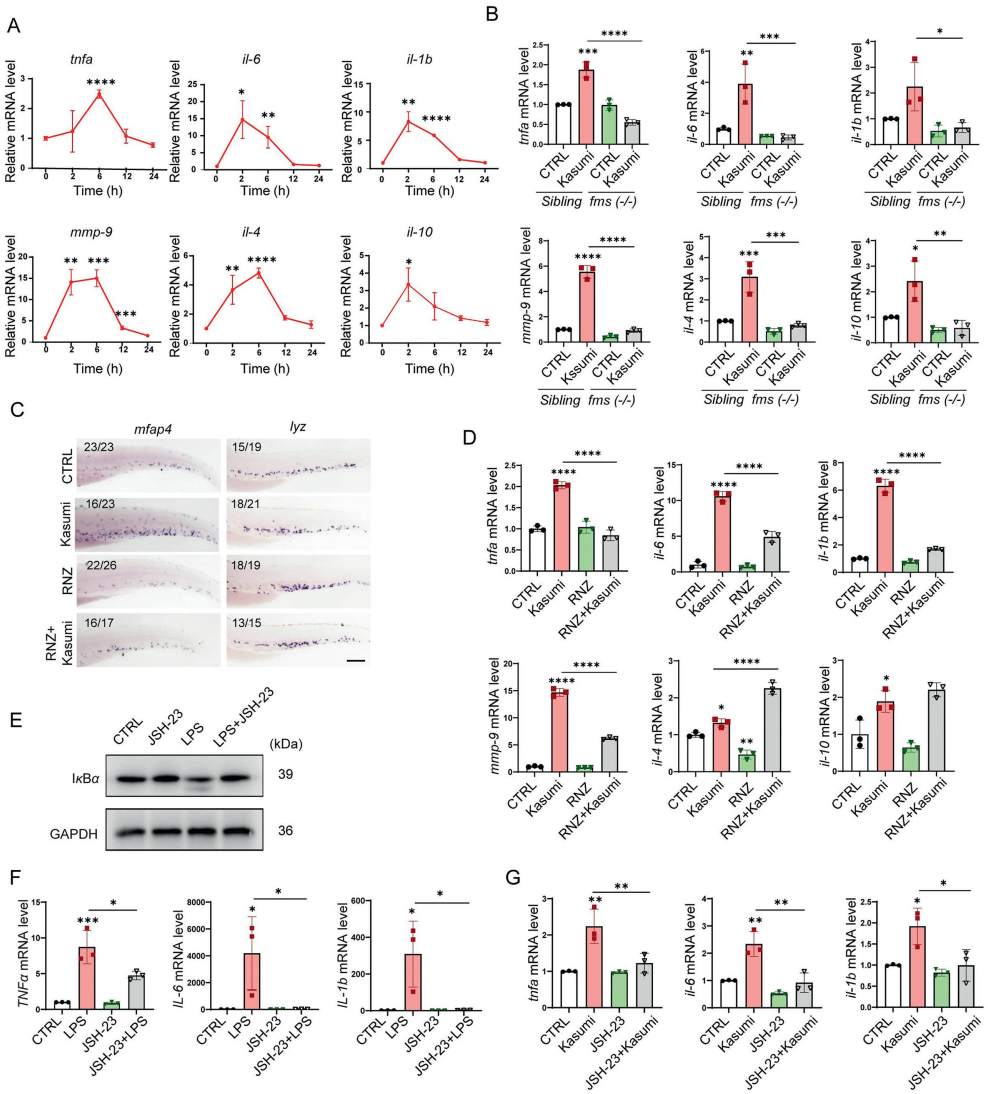

Fig. 2. Macrophages activated NFκB to produce inflammatory factors in leukemia-xenografted zebrafish. (A) Kasumi-1 cells were microinjected into zebrafish larvae at 2 dpf, then the mRNA expression of *tnfa*, *il-6*, *il-1b*, *mmp-9*, *il-4* and *il-10* in leukemic-xenograft zebrafish were determined by quantitative real-time polymerase chain reaction (qRT-PCR) at the indicated time points after transplantation. (B) The mRNA expression of *tnfa*, *il-6*, *il-1b*, *mmp-9*, *il-4* and *il-10* in *fms* mutants or siblings. (C) The expression of *mfap4* and *lyz* were detected by WISH in Tg(*mpeg1.1:GFP-NTR*) transgenic line treated with ronidazole for 36 h. Scale bar: 100 μm. (D) The mRNA expressions of *tnfa*, *il-6*, *il-1b*, *mmp-9*, *il-4* and *il-10* were detected by qRT-PCR after ronidazole (RNZ) mediated macrophage ablation. (E, F) RAW264.7 cells were pre-treated with 50 μmol/L JSH-23 before incubating with LPS, the protein expression of IκBα was detected by Western blot (E) and the mRNA expression of *TNF-α*, *IL-6*, and *IL-1b* (F) were analyzed after 24 h after LPS incubation. (G) The zebrafish larvae were pre-treated with or without JSH-23 before xenografting leukemia, the mRNA expression of *tnfa*, *il-6* and *il-1b* were analyzed at 24 hpi. GAPDH, glyceraldehyde-3-phosphate dehydrogenase. Data were expressed as mean ± SD ($n \geq 3$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

antioxidant [32]. In our previous study, we successfully synthesized poly(ferulic acid) nanoparticles (PFA NPs) using naturally derived ferulic acid, which exhibited remarkable potential as a self-therapeutic nanocarrier in cancer therapy [54]. In this study, PFA NPs was further used to deliver DOX for leukemia therapy. DOX was encapsulated in PFA polymer through simple and reproducible nanoprecipitation method. To be brief, PFA polymer, DOX, and stabilizer 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-[methoxy(polyethylene-glycol)-2000] (DSPE-PEG 2k) (all at 10 mg/mL in DMSO) were blended at a mass ratio of 4:1:2. Then, the mixture was slowly added drop by drop to the stirring water, resulting in the formation the DOX@PFA NP suspension. Next, the NP solution was concentrated through ultrafiltration at 2000 rpm. PFA NPs were prepared with the same procedure in the absence of DOX.

As shown in Figs. S3A and C (Supporting information), the resulting PFA NPs and DOX@PFA NPs exhibited sizes of approximately 100 nm and had a narrow polydispersity index (PDI), indicating a high degree of dispersion. Additionally, the surface charge of the nanoparticles transitioned from a negative charge (-21.9 ± 0.84 mV) to a positive charge (1.5 ± 0.43 mV) due to incorporation of positively charged DOX, confirming successful drug loading (Figs. S3B and D in Supporting information). DOX@PFA NPs with slightly positive surface charges tend to facilitate the uptake by tumor cells. Furthermore, both PFA NPs and DOX@PFA NPs exhibited a regular spherical structure, as visually confirmed by transmission electron microscope (Fig. S3E in Supporting information). To evaluate the stability of PFA NPs and DOX@PFA NPs, they were dispersed in phosphate buffered saline (PBS) measured by dynamic light scattering (DLS) for 7 days. As shown in Fig. S3F (Supporting information), the particle size of PFA NPs and DOX@PFA NPs showed no significant fluctuations during a long term, suggesting their good stability. The *in vitro* DOX release from NPs under different conditions was investigated by dial-

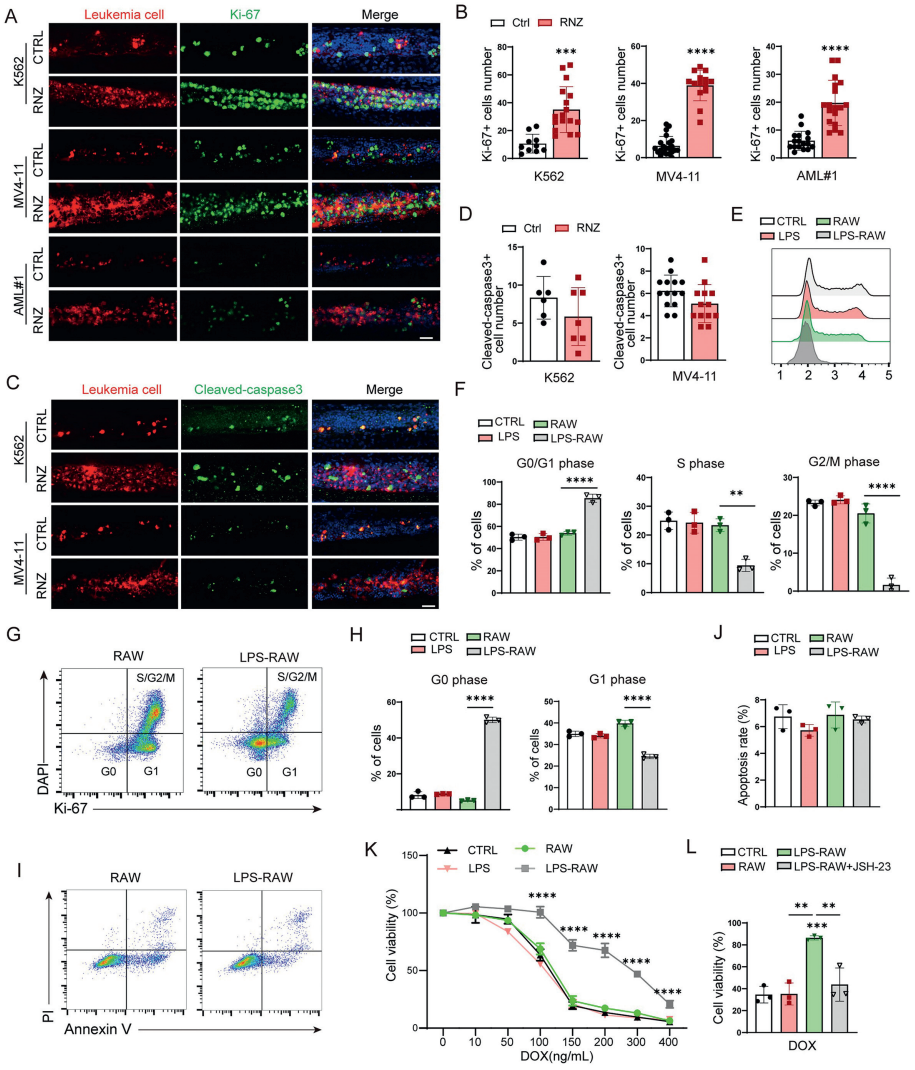

Fig. 3. Inflammatory factors induced leukemia chemoresistance by inhibiting cell cycle entry. (A–D) The CM-DiI labeled leukemia cells were transplanted into Tg(*mpeg1.1:GFP-NTR*) transgenic zebrafish with or without macrophage ablation. The proliferation and apoptosis of xenografted leukemia cells were examined by immunofluorescence staining with antibodies against Ki-67 (A) or cleaved caspase-3 (C). Scale bar: 20 μm. The number of Ki-67+ (B) and cleaved caspase-3+ (D) leukemic cells were counted respectively. Scale bar: 20 μm. (E, F) MV4-11 cells were incubated with supernatant from LPS-treated RAW264.7 cells, then the cell cycle of G0/G1 phase, S phase and G2/M phase were examined by flow cytometry *in vitro*. (G, H) Analyze the cell cycle distribution of G0 and G1 phase with Ki-67 and 4′,6-diamidino-2′-phenylindole (DAPI) staining. (I, J) Analysis of the apoptosis rate of leukemia cells by performing Annexin-V and propidium iodide (PI) double staining *in vitro*. The results showed that there were no difference on apoptosis rate among leukemia cells treated with medium, LPS, supernatant of normal or LPS-induced RAW264.7 cell. CCK-8 assays showed that leukemia cells treated with the supernatant of LPS-induced RAW264.7 cell had higher viability after treatment with DOX (K), but the cell viability was significantly reduced in JSH-23 pretreatment (L). Data were expressed as mean ± SD ($n \geq 3$). $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

ysis method. Neutral and acidic media were used to mimic physiological environment and tumor microenvironment, respectively. As shown in Fig. S3G (Supporting information), cumulative release of DOX from DOX@PFA NPs under acidic condition was higher than the release observed under neutral condition, with DOX release exceeding 80% under pH 5.0 at 72 h. This was primarily attributed to the accelerated degradation of PFA NPs under acidic environment. Thus, DOX@PFA NPs could effectively reach the weakly acidic tumor microenvironment, which facilitates to achieve the objectives of protecting DOX and enabling enhanced DOX release at tumor sites.

FA displays therapeutic effect on many diseases such as cardiovascular disease, cancer and Alzheimer's disease due to the ability to inhibit the expression of inflammatory cytokines [55]. We previously utilized PFA NPs as an optimal drug carrier to enhance the chemotherapeutic efficacy in colon cancer [54]. Here, we further respectively tested whether PFA NPs inhibits LPS- or leukemia-induced inflammation. RAW264.7 cells treated with LPS have decreased protein level of IκBα and increased mRNA expression of *IL-6* and *IL-1b*, while PFA NPs reversed the IκBα degradation and inflammatory factor production (Figs. 4A and B). We then traced the cellular localization of DOX@PFA NPs in leukemia-xenografted zebrafish model and found that DOX@PFA NPs fluorescent signals were highly accumulated in leukemia-induced inflammatory but not normal macrophages (Fig. 4C). Consistent with the *in vitro* results, PFA NPs treatment alleviated the expression of *il-6*, *il-1b* and *mmp9* induced by transplantation of Kasumi-1 cells into zebrafish larvae, but had no effect on the number of macrophages (Figs. 4D and E). Taken together, the uptake and accumulation of PFA NPs by inflammatory macrophages, along with their ability to suppress inflammatory factors in leukemia-xenografted zebrafish, suggest a targeted effect of PFA NPs on inflammatory macrophages.

To evaluate the cytotoxic effect of PFA NPs on leukemia cells, the cell viability of MV4–11, HL60, Kasumi-1 cells treated with PFA NPs alone were tested by Cell Counting Kit-8 (CCK-8) assay. As shown in Fig. S4A (Supporting information), PFA NPs did not

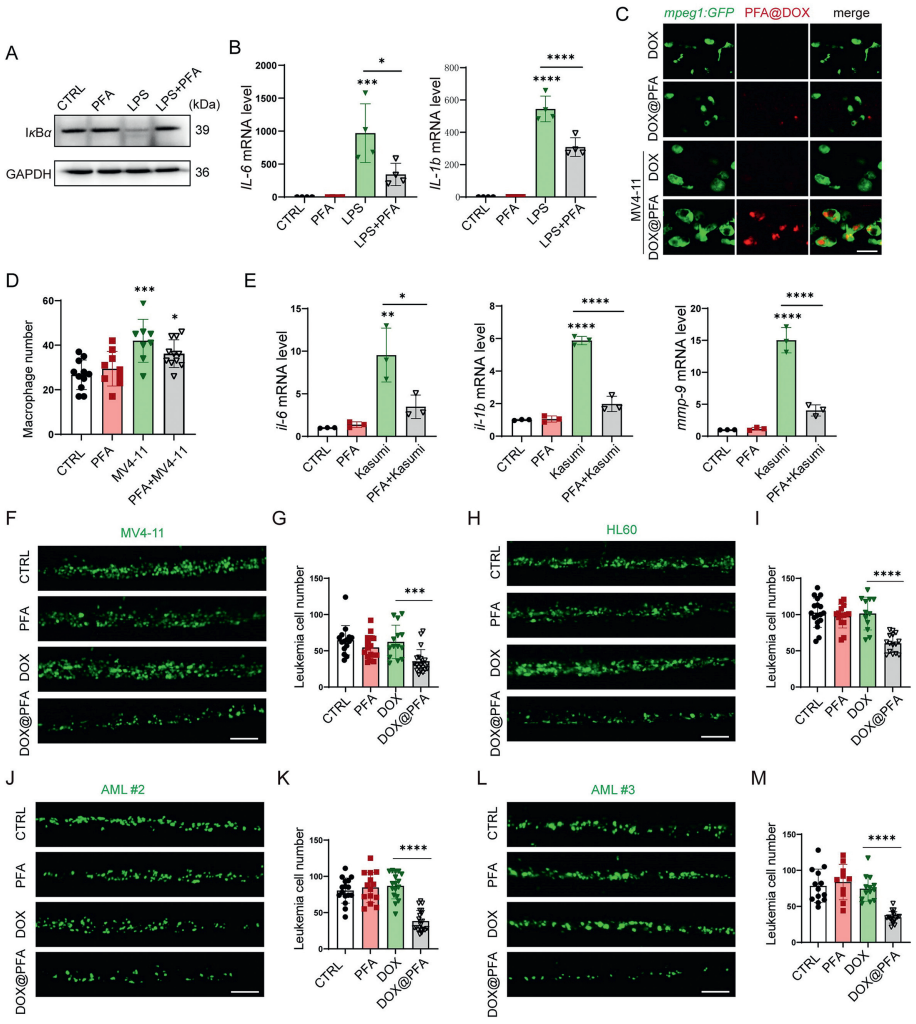

Fig. 4. PFA NPs targeted macrophages to inhibit inflammatory factors production. RAW264.7 cells were pretreated with 500 ng/mL PFA NPs for 24 h before LPS stimulus, then detected protein levels of IκBα with Western blot (A) and mRNA expressions of *IL-6* and *IL-1b* with qPCR (B). (C) Representative images of cellular uptake of PFA NPs in macrophages after DOX or DOX@PFA NPs treatment for 16 h in zebrafish. Scale bar: 20 μm. (D) Normal zebrafish or leukemic xenografted zebrafish were treated with DOX@PFA NPs for 48 h, the number of macrophages was quantified. (E) Normal or leukemic-xenograft zebrafish were treated with PFA NPs, and the mRNA expression of *il-6*, *il-1b* and *mmp-9* were determined by qRT-PCR. The Calcein labeled MV4–11 (H, I), HL60 (J, K), and primary AML cells from two patients (L–M) were xenografted into zebrafish larvae at 2 dpf. Scale bar: 100 μm. Then, xenografted zebrafish were treated with DMSO, PFA NPs, DOX, or DOX@PFA NPs for 48 h, and the number of leukemic cells in CHT were quantified. Data were expressed as mean ± SD ($n \geq 3$). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$.

affect leukemia cell viability at a wide range of concentrations. In addition, DOX or DOX@PFA NPs demonstrated similar leukemic cell viability *in vitro* (Fig. S4B in Supporting information), indicating that PFA NPs itself has no cytotoxicity towards AML. To evaluate the chemotherapy efficiency *in vivo*, we injected different sources of AML cells, including MV4-11 (Figs. 4F and G), HL60 (Figs. 4H and I), and primary cells from AML patients (Figs. 4J–M), into zebrafish hosts. Our results showed that the DOX-resistance AML cells were significantly eliminated by DOX@PFA NPs treatment. Taken together, these results indicate that the macrophage-targeting PFA nanocarrier alleviates inflammation and sensitizes AML cells to chemotherapy.

The inflammatory microenvironment plays a critical role in chemotherapy resistance, disease progression and relapse in AML [20,21,23]. However, the underlying mechanism of and therapeutic strategies against inflammation remain unclear. Our studies reveal that AML activate the CSF1R-NFκB pathway in macrophages to establish the inflammatory microenvironment. The inflammtroy factors derived from macrophages induced G0 phase arrest in leukemia cells, resulting in the development of chemoresistance. Furthermore, we have developed a macrophage-targeting poly(ferulic acid) based nanocarrier to mitigate inflammation and significantly enhance the chemotherapy efficacy in AML. In future studies, the PFA nanocarrier should be tested in AML mouse models and patient derived xenografts to further validate its anti-inflammatory and therapeutic potential.

Ethical statement

The use of the clinical specimens was approved by the Ethics Committee of the Sun Yat-sen Memorial Hospital in accordance with international guidelines and the ethical standards outlined in the Declaration of Helsinki.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2023.109422.

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