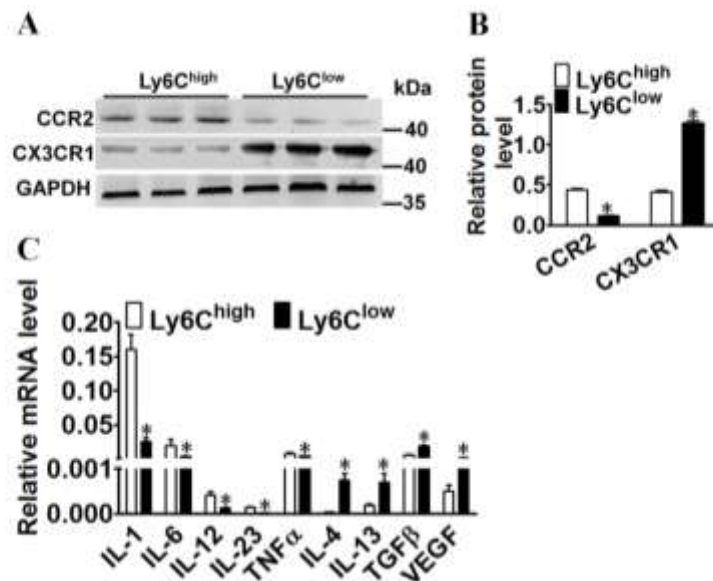


1 **Supplementary Figure 1**



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3 **Supplementary Figure 1. Characterization of Ly6C<sup>high</sup> and Ly6C<sup>low</sup> Mos/Mps.**

4 **A.** Western blot analysis of CCR2 and CX3CR1 expression in Ly6C<sup>high</sup> and Ly6C<sup>low</sup> Mos/Mps.

5 Mos/Mps were sorted from the peritoneal cavity in zymosan-challenged mice. **B.**

6 Densitometric quantification of CCR2 and CX3CR1 protein levels in Ly6C<sup>high</sup> and Ly6C<sup>low</sup>

7 Mos/Mps. \*P < 0.05 vs. Ly6C<sup>high</sup>, n = 6. **C.** mRNA expression of pro-inflammatory and

8 anti-inflammatory cytokines in Ly6C<sup>high</sup> and Ly6C<sup>low</sup> Mos/Mps. \*P < 0.05 vs. Ly6C<sup>high</sup>, n =

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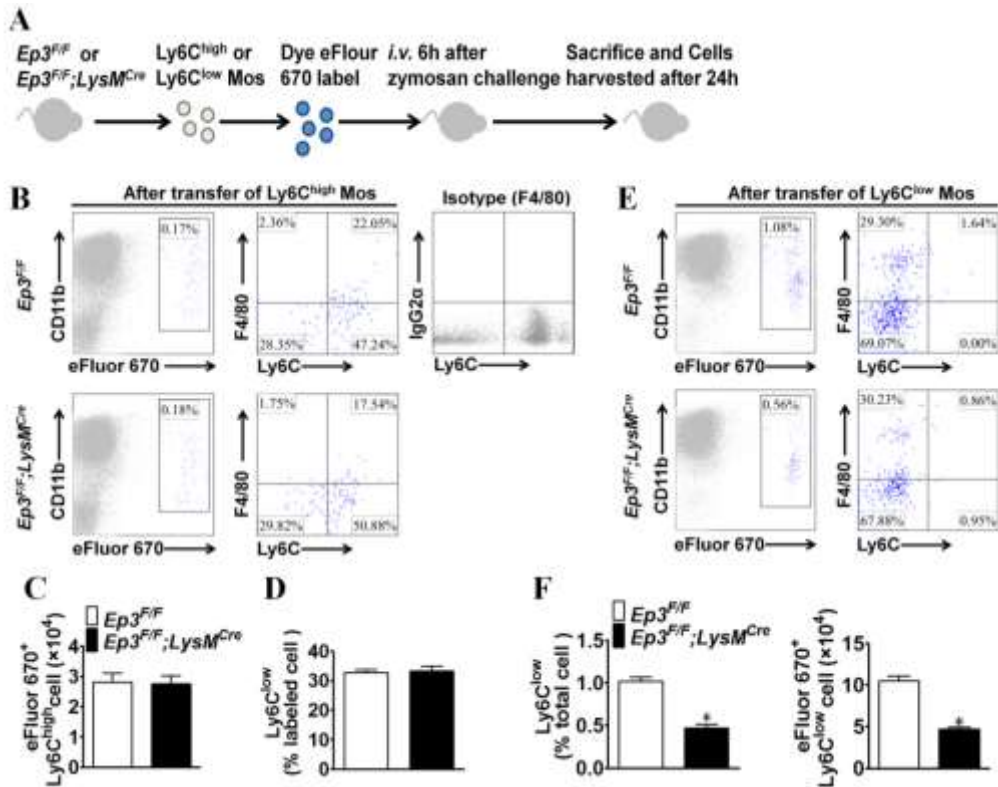
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21 **Supplementary Figure 2**

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24 **Supplementary Figure 2. Effect of *Ep3* deletion on peritoneal Mo differentiation in**  
 25 **zymosan-challenged mice.**

26 **A.** Illustration of experimental protocol with adoptive transfer of sorted  $Ly6C^{high}$  Mos ( $1 \times 10^6$ )  
 27 or  $Ly6C^{low}$  Mos ( $0.5 \times 10^6$ ) labeled with cell proliferation dye eFluor 670. **B.** Flow cytometric  
 28 analysis of peritoneal eFluor 670<sup>+</sup>Ly6C<sup>high</sup> Mos in zymosan-challenged mice. **C.**  
 29 Quantification of infiltrated eFluor 670<sup>+</sup>Ly6C<sup>high</sup> Mos/Mps as shown in **B.** n = 5-6. **D.**  
 30 Quantification of differentiated eFluor 670<sup>+</sup>Ly6C<sup>low</sup> Mos/Mps as shown in **B.** n=5-6. **E.** Flow  
 31 cytometric analysis of peritoneal eFluor 670<sup>+</sup>Ly6C<sup>low</sup> Mos in zymosan-challenged mice. **F.**  
 32 Percentage (Left) and total number (Right) of infiltrated eFluor 670<sup>+</sup>Ly6C<sup>low</sup> Mos/Mps were  
 33 calculated from **E.** \*P < 0.05 vs.  $Ep3^{F/F}$ , n = 5-6.

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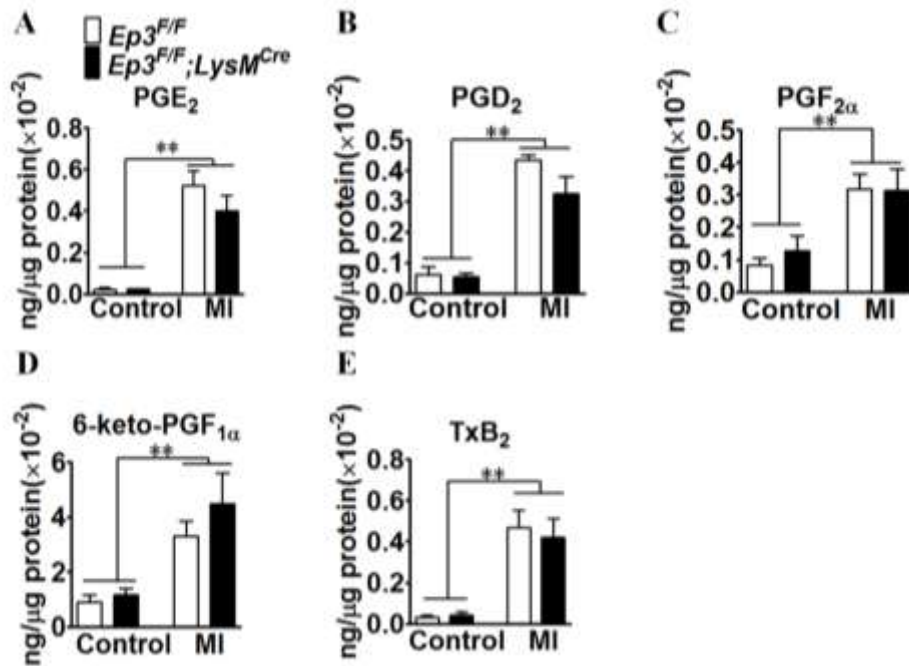
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40 **Supplementary Figure 3**

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43 **Supplementary Figure 3. PG production in ischemic hearts from  $Ep3^{F/F}$  and**  
44  **$Ep3^{F/F};LysM^{Cre}$  mice after MI.**

45 Mice underwent LAD ligation for 2 weeks, and then heart tissues were collected for PG  
46 extraction. **A-E.**  $PGE_2$  (**A**),  $PGD_2$  (**B**),  $PGF_{2\alpha}$  (**C**), 6-keto- $PGF_{1\alpha}$ , a stable hydrolyzed product  
47 of  $PGI_2$  (**D**), and  $TxB_2$  (**E**) were examined by LC/MS/MS. \*\* $P < 0.01$ ,  $n = 5$ .

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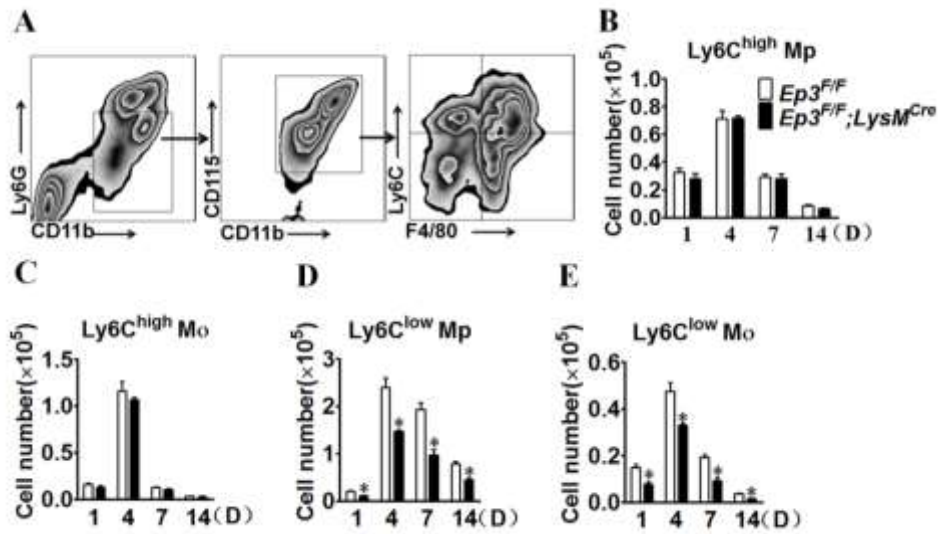
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58 **Supplementary Figure 4**

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61 **Supplementary Figure 4. Ep3 deletion reduces recruitment of Ly6C<sup>low</sup> Mos /Mps.**

62 **A.** Gating strategy for CD11b<sup>+</sup>CD115<sup>+</sup>Ly6G<sup>+</sup>F4/80<sup>-</sup>Ly6C<sup>high</sup> Mos, CD11b<sup>+</sup>CD115<sup>+</sup> Ly6G<sup>-</sup>  
 63 F4/80<sup>-</sup>Ly6C<sup>low</sup> Mos, CD11b<sup>+</sup>CD115<sup>+</sup>Ly6G<sup>-</sup>F4/80<sup>+</sup>Ly6C<sup>high</sup> Mps, CD11b<sup>+</sup>CD115<sup>+</sup> Ly6G<sup>-</sup> F4/80<sup>+</sup>  
 64 Ly6C<sup>high</sup> Mps in hearts after left anterior descending (LAD) artery ligation in mice. **B-D.**  
 65 Effect of *Ep3* deletion on number of Ly6C<sup>high</sup> Mps (**B**), Ly6C<sup>high</sup> Mos (**C**), Ly6C<sup>low</sup> Mps (**D**)  
 66 and Ly6C<sup>low</sup> Mos (**E**) in injured hearts of mice after MI. \*P < 0.05 vs. *Ep3<sup>F/F</sup>*, n = 5-6.

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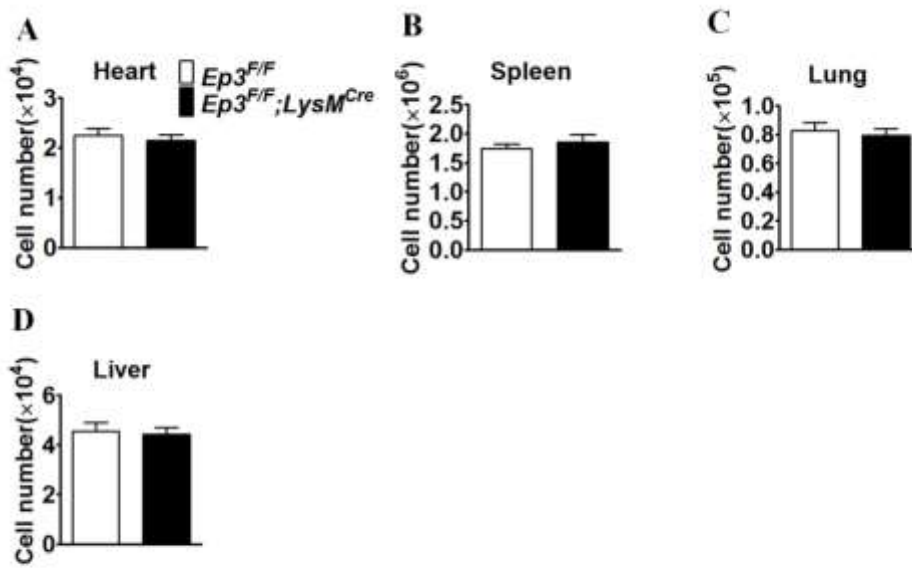
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79 **Supplementary Figure 5**

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82 **Supplementary Figure 5. Effect of myeloid-*Ep3* deficiency on residential Mps in mice**

83 Effect of *Ep3* deletion on total residential Mps in heart (A), spleen (B), lung (C), liver (D). n =  
84 5-6.

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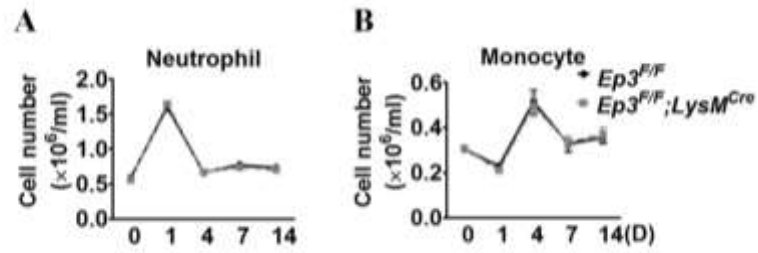
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96 **Supplementary Figure 6**

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99 **Supplementary Figure 6. Effect of myeloid-*Ep3* deficiency on circulating Mos and**  
100 **neutrophils in mice.**

101 Quantification of plasma Mos (A) and neutrophils(B) in mice before and after MI at different  
102 timepoints. n =5.

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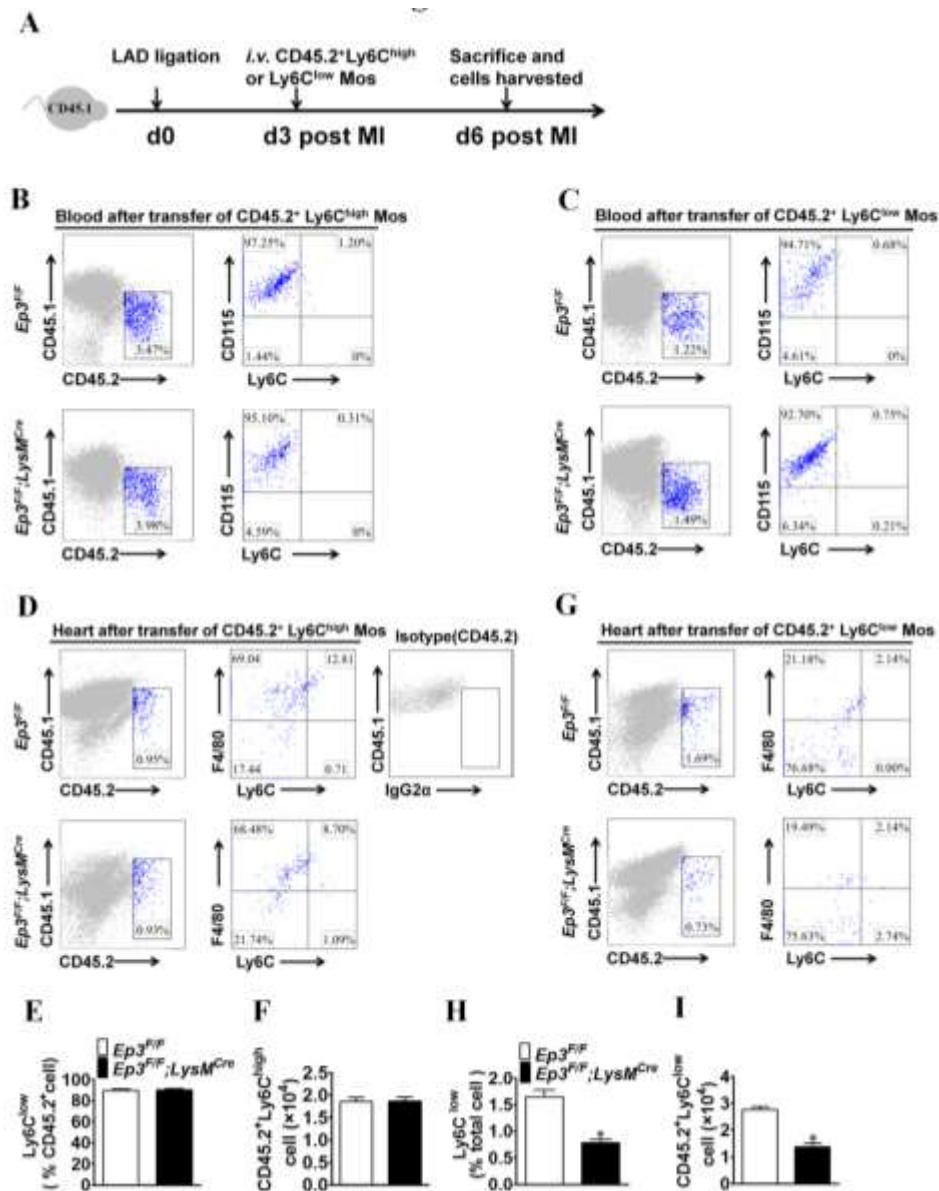
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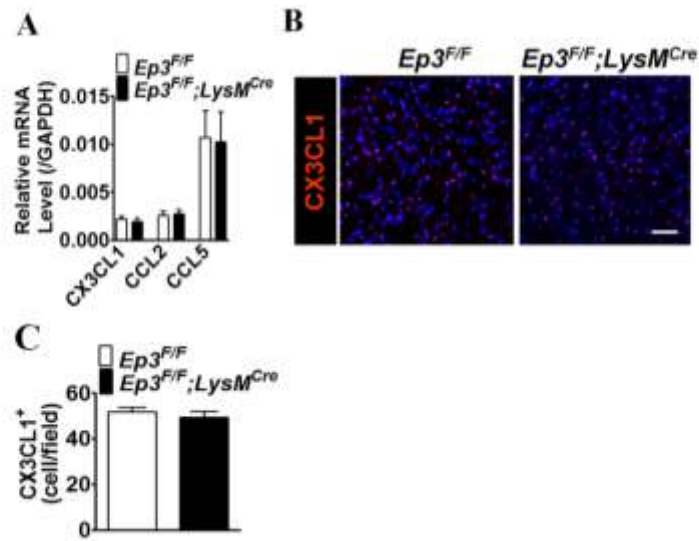
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121 **Supplementary Figure 7. Effect of *Ep3* deletion on Mo differentiation in infarcted**  
 122 **hearts in mice.**

123 **A.** Illustration of experimental approach with separate adoptive transfer of sorted  
 124 CD45.2<sup>+</sup>Ly6C<sup>high</sup> Mos (1×10<sup>6</sup>) and CD45.2<sup>+</sup>Ly6C<sup>low</sup> Mos (0.5×10<sup>6</sup>) in *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and  
 125 *Ep3<sup>F/F</sup>* (CD45.1<sup>+</sup>) mice 3 days after MI. **B.** Flow cytometric analysis of blood CD45.2<sup>+</sup>  
 126 Ly6C<sup>high</sup> Mos from *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice. **C.** Flow cytometric analysis of blood  
 127 CD45.2<sup>+</sup>Ly6C<sup>low</sup> Mos from *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice. **D.** Flow cytometric analysis of  
 128 cardiac CD45.2<sup>+</sup>Ly6C<sup>high</sup> Mos in *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice after MI on day 3 after  
 129 adoptive transfer. **E.** Quantification of differentiated CD45.2<sup>+</sup>Ly6C<sup>low</sup> Mos/Mps as shown in  
 130 **D.** n=4-5. **F.** Quantification of infiltrated CD45.2<sup>+</sup>Ly6C<sup>high</sup> Mos/Mps as shown in **D.** n=4-5.  
 131 n=4-5. **G.** Flow cytometric analysis of cardiac CD45.2<sup>+</sup>Ly6C<sup>low</sup> Mos in *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and  
 132 *Ep3<sup>F/F</sup>* mice after MI on day 3 after adoptive transfer. Percentage (**H**) and total number (**I**) of  
 133 infiltrated CD45.2<sup>+</sup>Ly6C<sup>low</sup> Mos/Mps were calculated from **G.** \*P < 0.05 vs. EP3<sup>F/F</sup>, n = 4-5.

134 **Supplementary Figure 8**

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137 **Supplementary Figure 8. Effect of *Ep3* deficiency on *CX3CR1* ligand in infarcted**  
138 **hearts in mice.**

139 **A.** Relative mRNA levels of chemokine ligand *CX3CL1*, *CCL2* and *CCL5* in the infarcted  
140 hearts from *EP3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice at day 14 after MI. n=5. **B.** Representative  
141 CX3CL1 staining images of the infarcted hearts from *Ep3<sup>F/F</sup>;Lys<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice at 14  
142 after MI. n=5. Scale bar, 20  $\mu$ m. **C.** Quantification of CX3CL1<sup>+</sup> cells in the infarcted hearts  
143 shown in B. n=5.

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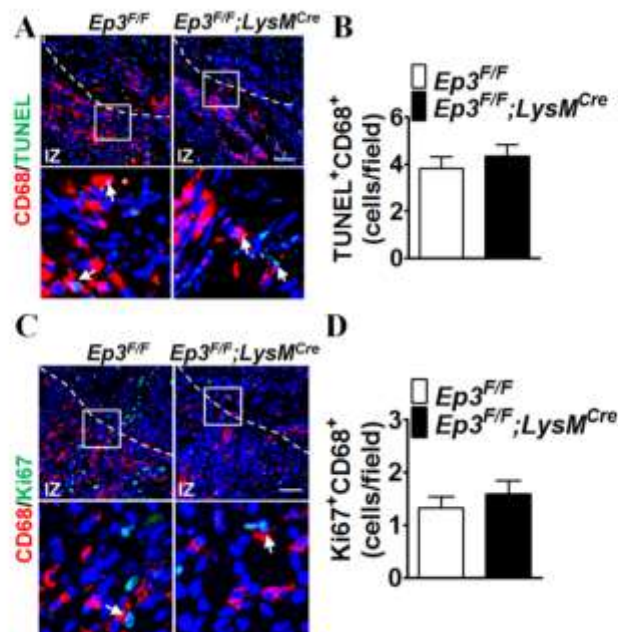
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164 **Supplementary Figure 9**

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167 **Supplementary Figure 9. Effect of *Ep3* deficiency in proliferation and apoptosis of**  
 168 **Mps infiltrated in infarcted hearts.**

169 **A.** Representative TUNEL<sup>+</sup>CD68<sup>+</sup> cell staining images of the infarcted hearts from  
 170 *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice at day 7 after MI. Scale bar, 50µm. IZ, infarct zone. **B.**  
 171 Quantification of TUNEL<sup>+</sup>CD68<sup>+</sup> cells in infarcted hearts at day 7 after MI. n=5. **C.**  
 172 Representative Ki67<sup>+</sup>CD68<sup>+</sup> cell staining images of infarcted hearts from *EP3<sup>F/F</sup>;LysM<sup>Cre</sup>* and  
 173 *Ep3<sup>F/F</sup>* mice at day 7 after MI. Scale bar, 50 µm. **D.**Quantification of Ki67<sup>+</sup> CD68<sup>+</sup> cells in  
 174 infarcted hearts at day 7 after MI. n=5.

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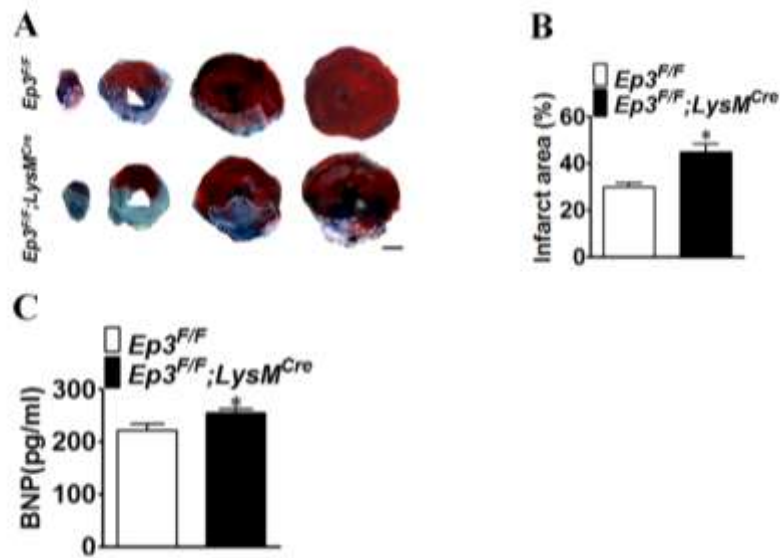
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184 **Supplementary Figure 10**

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187 **Supplementary Figure 10. *Ep3* deficiency in Mos/Mps increases infarct size in mice**  
188 **after MI.**

189 **A.** Representative images of Evans blue and triphenyltetrazolium chloride staining on heart  
190 sections from  $Ep3^{F/F}$  and  $Ep3^{F/F};LysM^{Cre}$  mice two weeks after MI. The dotted line denotes the  
191 infarct zone. Scale bar, 1 mm. **B.** Infarct sizes were quantitated as shown in A. \* $P < 0.05$  vs.  
192  $Ep3^{F/F}$ ,  $n = 5$ . **C.** Brain natriuretic protein (BNP) was measured by enzyme-linked  
193 immunosorbent assay. \* $P < 0.05$  vs.  $Ep3^{F/F}$ ,  $n = 10$ .

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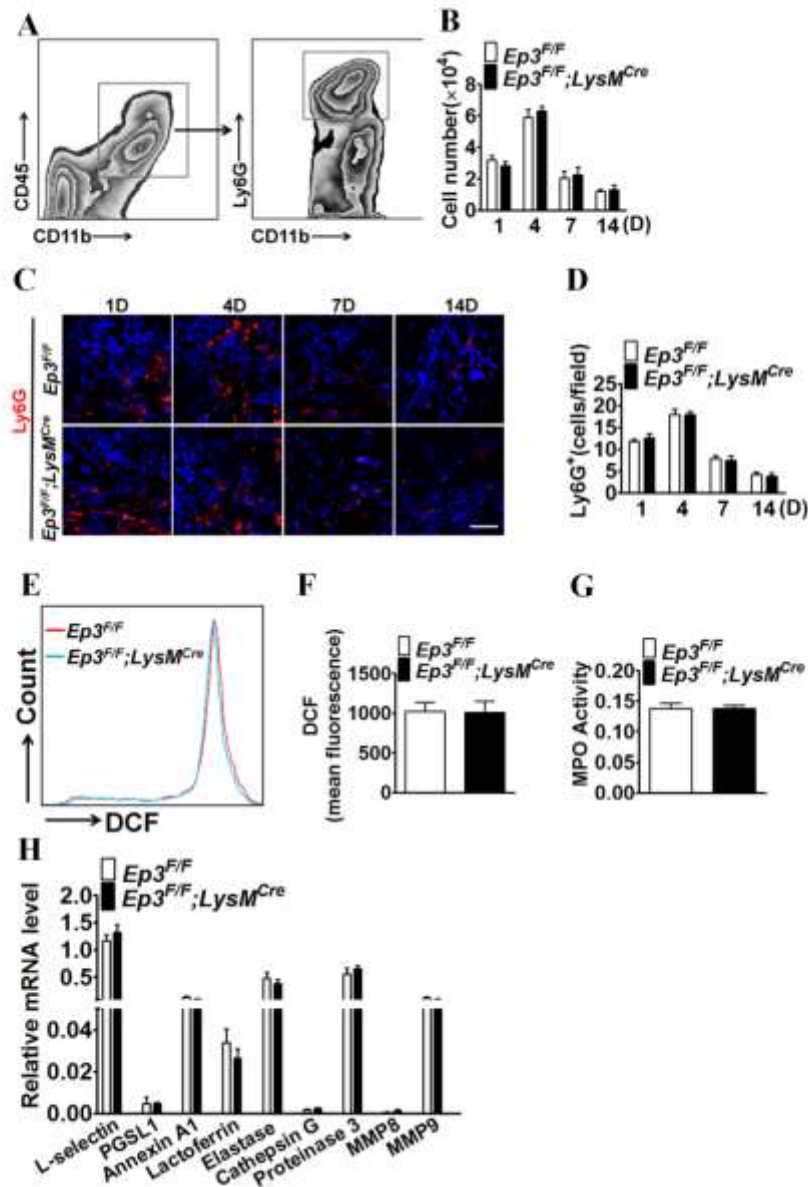
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209 **Supplementary Figure 11. Effect of *Ep3* deletion on neutrophil infiltration in hearts**  
 210 **after MI.**

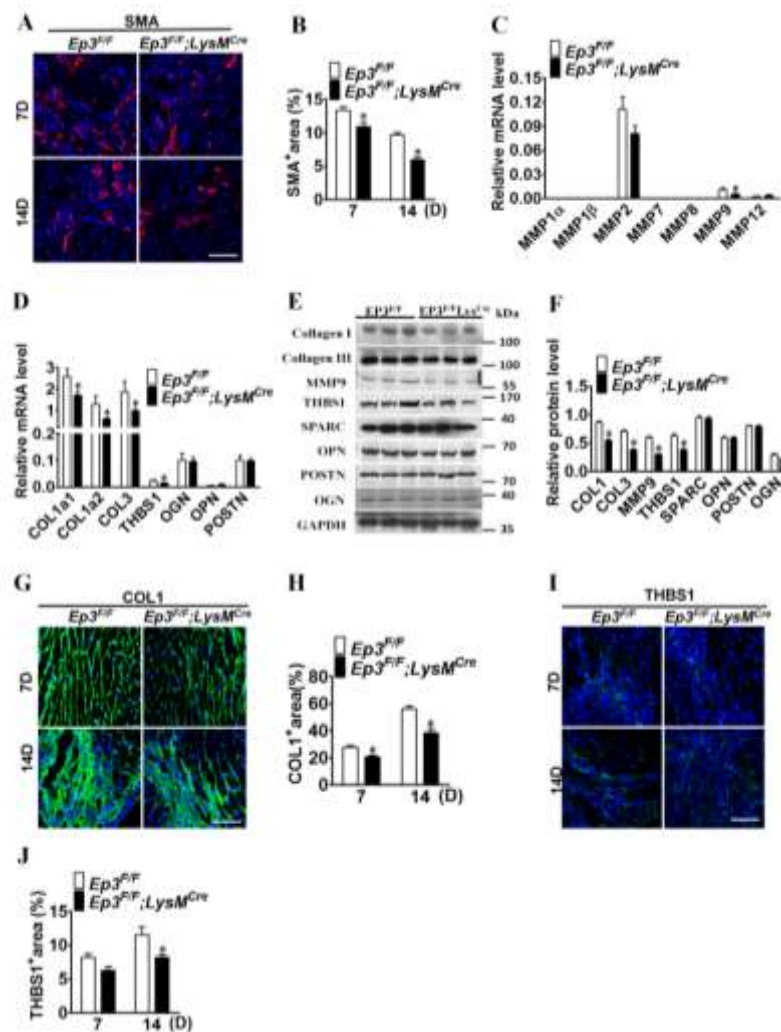
211 **A.** Gating strategy for neutrophils in hearts from mice after MI. **B.** Effect of myeloid cell-*Ep3*  
 212 deletion on neutrophil infiltration in infarcted hearts at different timepoints. n=6. **C.**  
 213 Representative Ly6G<sup>+</sup> cell staining images of the infarcted hearts from *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and  
 214 *Ep3<sup>F/F</sup>* mice after MI. Scale bar, 50 μm. **D.** Quantification of Ly6G<sup>+</sup> cells in infarcted hearts.  
 215 n=5. **E-F** ROS levels in neutrophils isolated from infarcted hearts at day 3 after MI. n=4. **G**  
 216 MPO expression in neutrophils isolated from infarcted hearts day 3 after MI. n=4. **H.** Relative  
 217 mRNA levels of surface makers, proteases and matrix metallopeptidases of neutrophils isolated  
 218 from infarcted hearts at day 3 after MI. n=4.

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221 **Supplementary Figure 12**

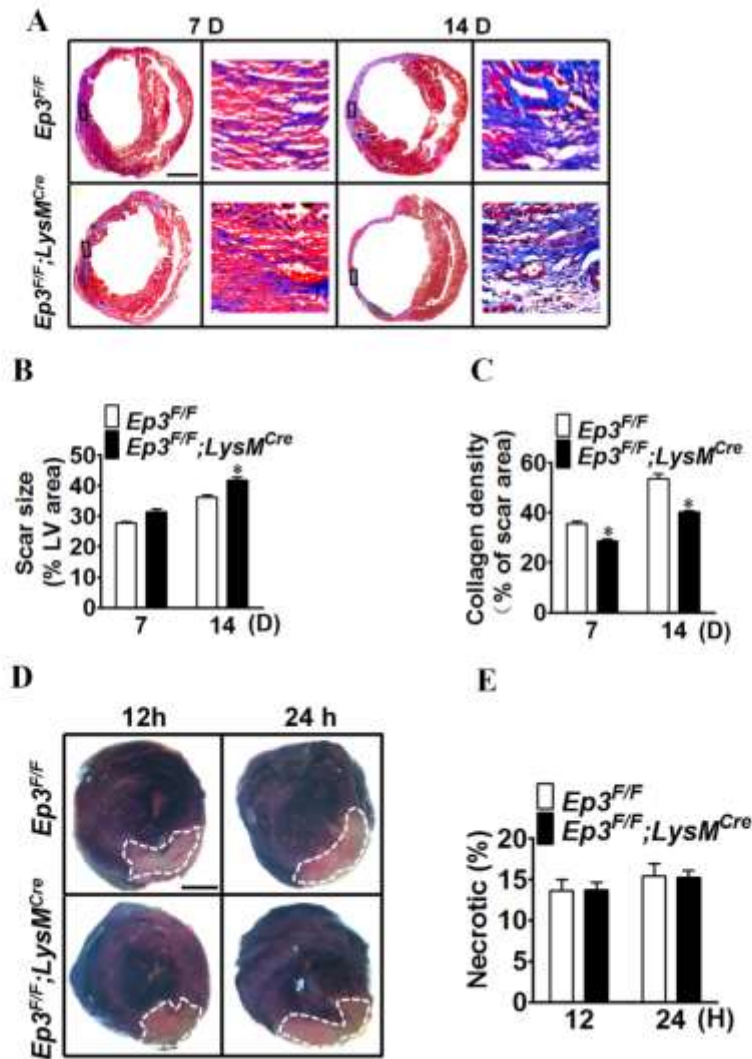
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224 **Supplementary Figure 12. Adverse cardiac remodelling in  $Ep3^{F/F};LysM^{Cre}$  mice after**  
 225 **MI**

226 **A.** Representative SMA staining images of the infarcted hearts from  $Ep3^{F/F};LysM^{Cre}$  and  
 227  $Ep3^{F/F}$  mice at day 7 and 14 after MI. **B.** Quantification of SMA staining shown in **A**. \*P <  
 228 0.05 vs.  $Ep3^{F/F}$ , n = 6. Scale bar, 50  $\mu$ m. **C.** Relative mRNA levels of MMPs in the infarcted  
 229 hearts from  $Ep3^{F/F};LysM^{Cre}$  and  $Ep3^{F/F}$  mice at day 14 after MI. \*P < 0.05 vs.  $Ep3^{F/F}$ , n = 6. **D.**  
 230 Relative mRNA levels of fibrotic genes in the infarcted hearts from  $Ep3^{F/F};LysM^{Cre}$  and  
 231  $Ep3^{F/F}$  mice at day 14 after MI. \*P < 0.05 vs.  $Ep3^{F/F}$ , n = 6. **E.** Western blot analysis of  
 232 MMP9 and fibrotic proteins in the infarcted hearts from  $Ep3^{F/F};LysM^{Cre}$  and  $Ep3^{F/F}$  mice at  
 233 day 14 after MI. **F.** Quantification of MMP9 and fibrotic protein expression shown in **E**. \*P <  
 234 0.05 vs.  $Ep3^{F/F}$ , n = 6. **G.** Representative collagen I staining images in the infarcted hearts  
 235 from  $Ep3^{F/F};LysM^{Cre}$  and  $Ep3^{F/F}$  mice at day 7 and 14 after MI. **H.** Quantification of collagen I  
 236 staining shown in **G**. \*P < 0.05 vs.  $Ep3^{F/F}$ , n = 6. Scale bar, 50  $\mu$ m. **I.** Representative THBS1  
 237 staining images of the infarcted hearts from  $Ep3^{F/F};LysM^{Cre}$  and  $Ep3^{F/F}$  mice at day 7 and 14  
 238 after MI. Scale bar, 50  $\mu$ m. **J.** Quantification of THBS1 staining shown in **I**. \*P < 0.05 vs.  
 239  $Ep3^{F/F}$ , n = 6.



242 **Supplementary Figure 13. Effect of myeloid-Ep3 deficiency on scar formation and**  
 243 **necrosis in mice after MI.**  
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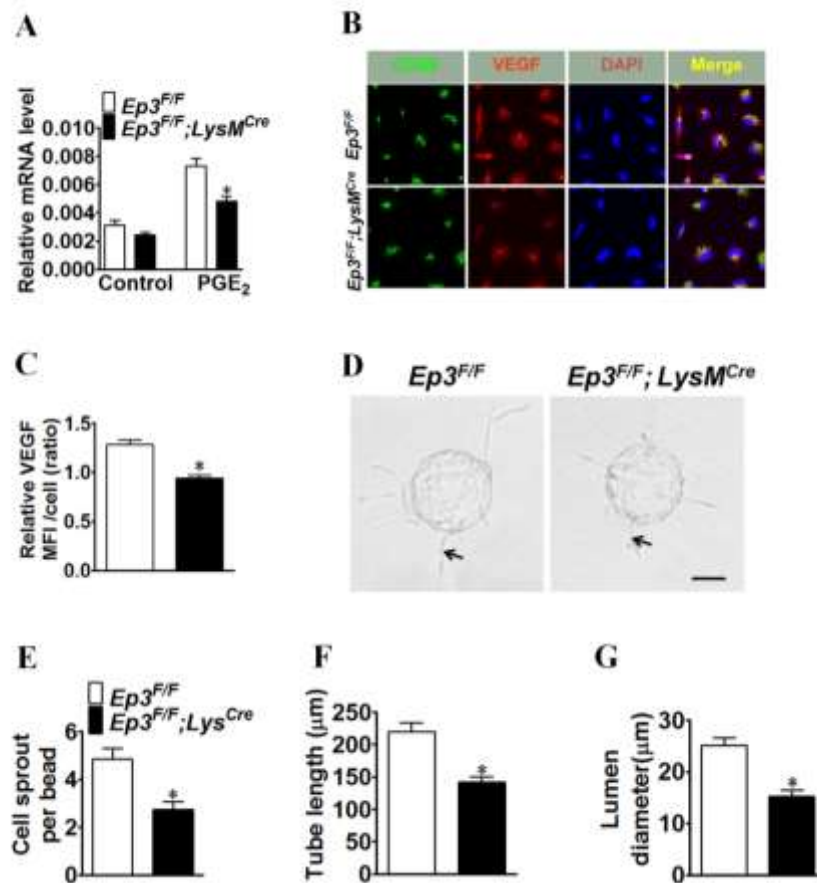
245 **A.** Representative Masson's trichrome staining images of heart cross sections (2.0 mm  
 246 distance from ligation site). from *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice at day 7 and 14 after MI.  
 247 Scale bar, 1mm. **B.** Quantification of collagen I density within scar area shown in **A**. \*P < 0.05  
 248 vs. *Ep3<sup>F/F</sup>*, n = 6. **C.** Quantification of scar size in infarcted hearts shown in **A**. \*P < 0.05 vs.  
 249 *Ep3<sup>F/F</sup>*, n = 6. **D.** Representative NBT staining images of heart sections ( mid-papillary muscle  
 250 level) from *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice 12 hours and 24 hours after LAD ligation. Scale  
 251 bar, 1mm. **E.** Quantification of necrotic areas in infarcted hearts shown in **D**. n = 5.

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259 **Supplementary Figure 14.Mp *Ep3* deficiency reduces VEGF secretion and tube**  
 260 **formation of co-cultured human vascular endothelial cells (HUVECs) *in vitro*.**

261 **A.** *VEGF* mRNA expression levels in peritoneal Mos/MPs from *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>*  
 262 mice. \*P < 0.05 vs. *Ep3<sup>F/F</sup>*, n = 10. **B.** Representative immunostaining of CD68 (green) and  
 263 VEGF (red) in peritoneal Mps from *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice. Scale bar, 20 μm. **C.**  
 264 Quantitation of VEGF signaling in CD68<sup>+</sup> cells in Mos/MPs as shown in (B). \*P < 0.05 vs.  
 265 *Ep3<sup>F/F</sup>*, n = 6. **D-G.** Fibrin bead-bound HUVECs were co-cultured with Mps from  
 266 *Ep3<sup>F/F</sup>;LysM<sup>Cre</sup>* and *Ep3<sup>F/F</sup>* mice, and multiple capillary-like sprouts were displayed on day 7  
 267 (D). Black arrow, capillary-like sprout; scale bar, 20 μm. The number of vessel sprouts per  
 268 bead (E), the lumen diameter (F), and single-tube length per bead (G) were quantified at day 7.  
 269 \*P < 0.05 vs. *Ep3<sup>F/F</sup>*, n = 4.

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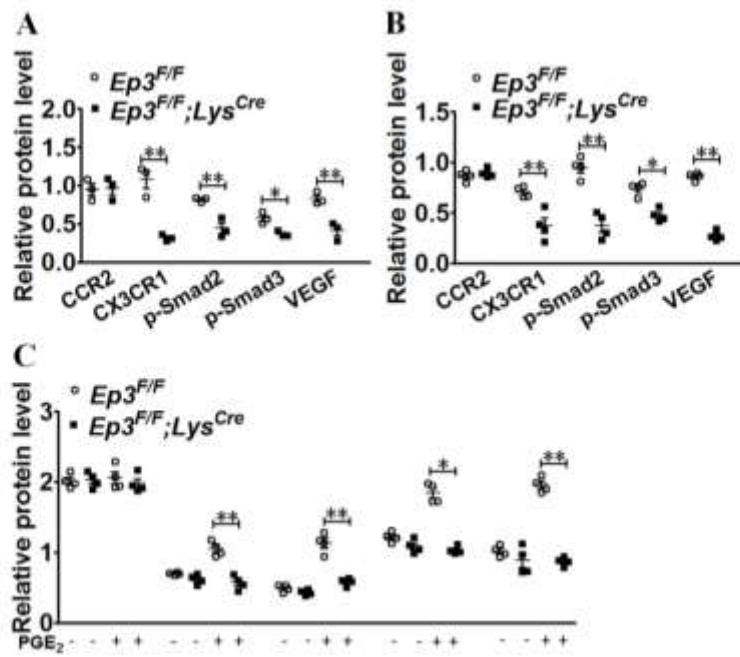
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275 **Supplementary Figure 15**

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278 **Supplementary Figure 15. Effect of *Ep3* deletion on expression of CCR2 and CX3CR1**  
 279 **and TGFβ1 signaling in Mps.**

280 A-C. Densitometric quantification of CCR2, p-Smad2/3, CX3CR1, and VEGF protein  
 281 expression of peritoneal Mps from in zymosan-challenged mice, as shown in Figure 5A-5C.  
 282 \*P < 0.05 vs. *Ep3<sup>F/F</sup>*, n = 3-4.

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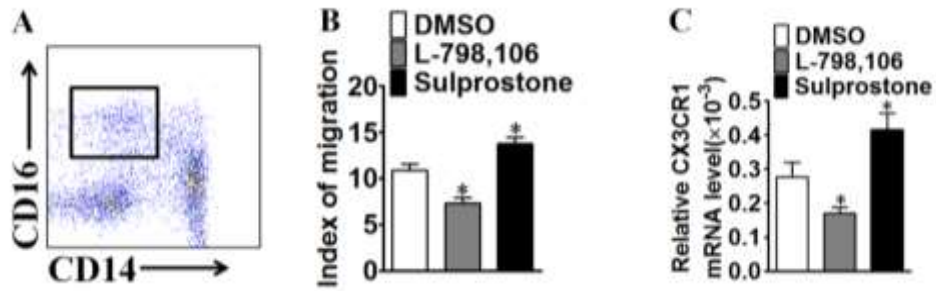
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293 **Supplementary Figure 16**

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296 **Supplementary Figure 16. Effect of Inhibition or activation of *Ep3* receptor on**  
297 ***CX3CR1* expression and migration of human CD14<sup>dim</sup> CD16<sup>+</sup> Mos.**

298 **A.** Gating strategy for CD14<sup>dim</sup>CD16<sup>+</sup> cells from human PBMCs. **B.** Effect of Sulprostone or  
299 L798, 106 treatment on CD14<sup>dim</sup>CD16<sup>+</sup> Mos migration. \*P < 0.05 vs. DMSO; n = 3-4. **C.**  
300 Effect of Sulprostone or L798,106 treatment on *CX3CR1* expression of CD14<sup>dim</sup>CD16<sup>+</sup> Mos.  
301 \*P < 0.05 vs. DMSO; n = 5.

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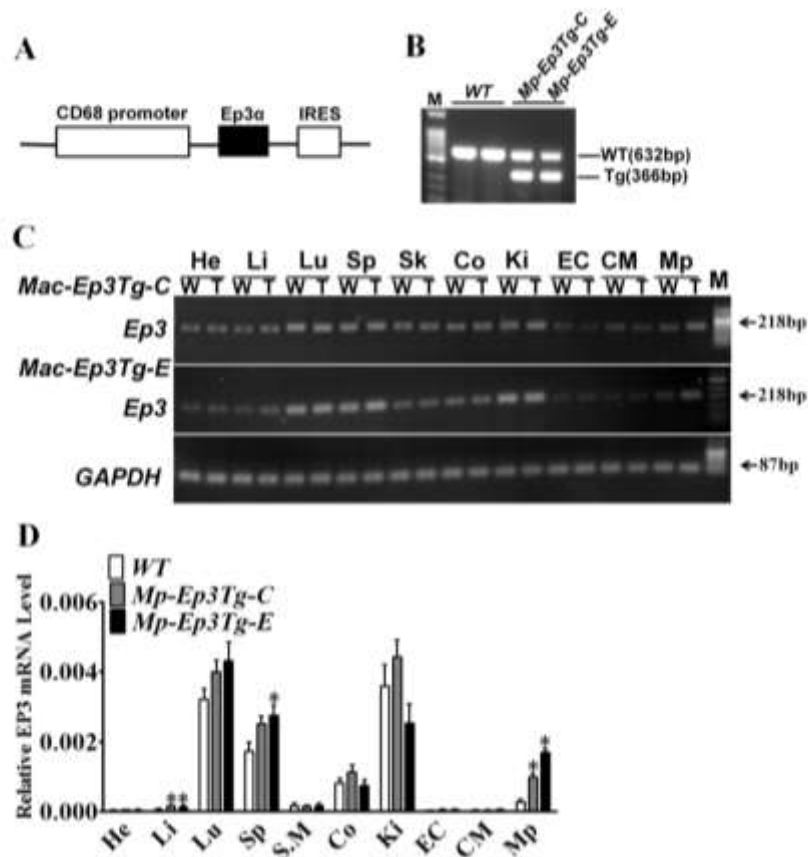
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319 **Supplementary Figure 17. Characterization of Ep3α transgenic mice**

320 **A.** Transgenic construct for CD68 promoter-driven *Ep3α* expression. **B.** Genotyping of *Mac-*  
 321 *Ep3α-Tg* mice. M, marker; TG, transgenic mice. **C.** Analysis of *Ep3* expression levels in  
 322 different tissues from *Mp-Ep3Tg* mice by gel electrophoresis of RT-PCR products. He, heart;  
 323 Li, liver; Lu, lung; Sp, spleen; S.M, skeletal muscle; Co, colon; Ki, kidney; EC, endothelial  
 324 cell; CM, cardiomyocyte cell; Mp, macrophage. W, WT mice; T, transgenic mice. **D.** Relative  
 325 *Ep3* mRNA expression levels in different tissues from *Mp-Ep3Tg* mice. \*\*P < 0.05 vs.  
 326 wild-type (WT), n = 6.

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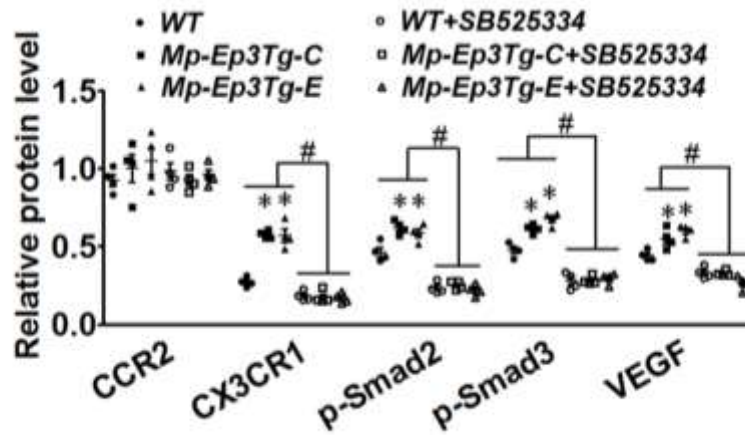
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333 **Supplementary Figure 18**

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336 **Supplementary Figure 18.** Densitometric quantification of CCR2, p-Smad2/3, CX3CR1,

337 and VEGF protein expression of peritoneal Mps after treatment from overexpression mice, as

338 shown in Figure 5H. \*P < 0.05 vs. WT, #P < 0.05 vs. Control, n = 4.

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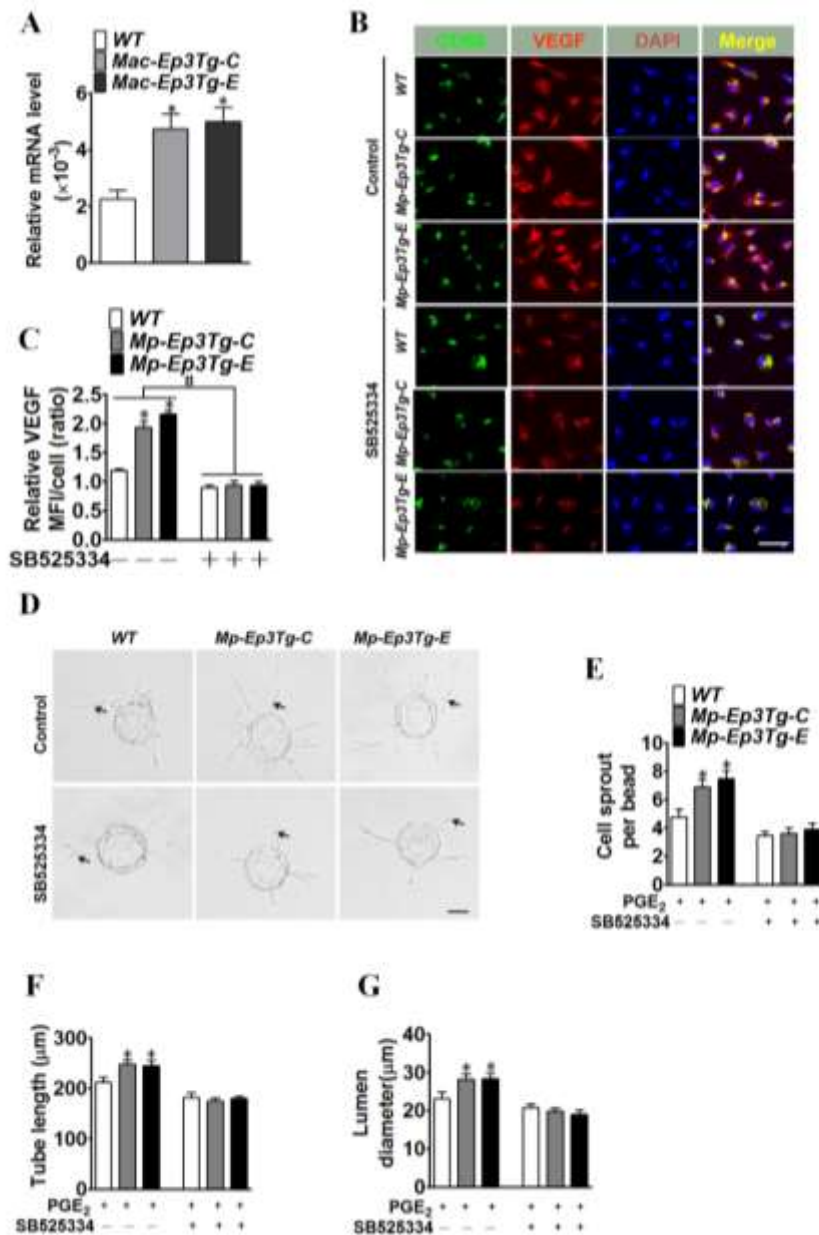
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 369 **Supplementary Figure 19. Mp-Ep3 overexpression enhances VEGF secretion and tube**  
 370 **formation of co-cultured HUVECs *in vitro*.**

371 A. *VEGF* mRNA expression level in peritoneal Mos/Mps from *WT*, *Mp-Ep3Tg-C*, and  
 372 *Mp-Ep3Tg-E* mice. \* $P < 0.05$  vs. *WT*,  $n = 10$ . **B.** Representative immunostaining of CD68  
 373 (green) and VEGF (red) in peritoneal Mps from *WT*, *Mp-Ep3Tg-C*, and *Mp-Ep3Tg-E* mice  
 374 mice. Scale bar, 20  $\mu\text{m}$ . **C.** Quantitation of VEGF signaling in CD68<sup>+</sup> cells in Mos/MPs, as  
 375 shown in (**B**). \* $P < 0.05$  vs. *WT*, # $P < 0.01$  as indicated,  $n = 6-7$ . **D-G.** Fibrin bead-bound  
 376 HUVECs were co-cultured with Mps from *WT*, *Mp-Ep3Tg-C*, and *Mp-Ep3Tg-E* mice, and  
 377 multiple capillary-like sprouts were displayed at day 7 (**D**). Black arrow, capillary-like sprout.  
 378 Scale bar, 20  $\mu\text{m}$ . The number of vessel sprouts per bead (**E**), the lumen diameter (**F**), and  
 379 single-tube length per bead (**G**) were quantified at day 7. \* $P < 0.05$  vs. *WT*,  $n = 4$ .

Figure 5 A

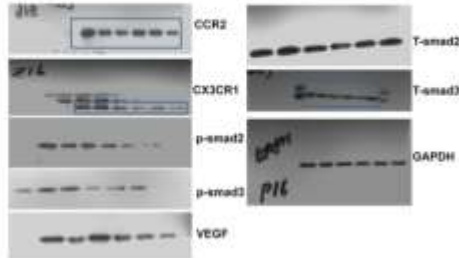


Figure 5B

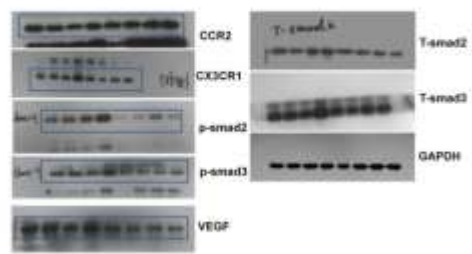


Figure 5C

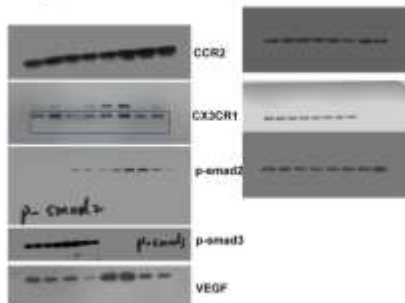


Figure 5H

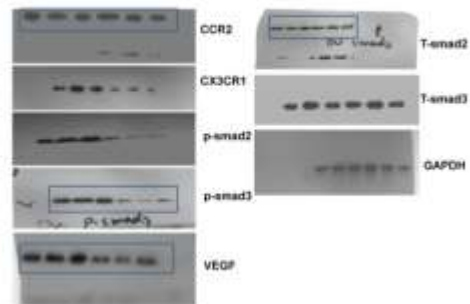
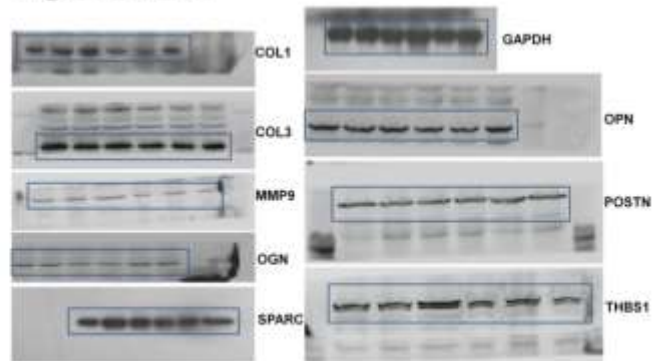


Figure S1A



Figure S12E



394 **Supplementary Tables**395 **Supplementary Table 1. Effect of Mo/Mp Ep3 deletion on cardiac recovery after MI in**  
396 **mice**

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	Sham		MI	
	Ep3 <sup>F/F</sup>	Ep3 <sup>F/F</sup> ;LysM <sup>Cre</sup>	Ep3 <sup>F/F</sup>	Ep3 <sup>F/F</sup> ;LysM <sup>Cre</sup>
LVESD(mm)	3.03±0.13	2.71±0.11	4.18±0.22 <sup>#</sup>	5.48±0.29 <sup>*,#</sup>
LVEDD(mm)	4.22±0.10	4.02±0.08	4.86±0.15 <sup>#</sup>	5.82±0.26 <sup>*,#</sup>
LVESV(μl)	37.77±3.22	29.91±2.47	81.79±9.8 <sup>#</sup>	152.53±17.96 <sup>*,#</sup>
LVEDV(μl)	78.00±4.81	71.28±3.28	112.6±8.26 <sup>#</sup>	173.15±17.86 <sup>*,#</sup>
FS(%)	28.45±1.92	32.45±2.38	14.53±2.23 <sup>#</sup>	6.21±1.01 <sup>*,#</sup>
SV(%)	43.07±1.94	43.08±2.77	30.81±3.21 <sup>#</sup>	20.61±1.53 <sup>*,#</sup>
CO(ml/min)	17.02±1.45	17.43±1.97	11.96±1.73 <sup>#</sup>	9.21±1.30 <sup>*,#</sup>
HR(BPM)	391.81±7.93	401.3±6.99	389.75±6.38	405.18±6.87
BW (g)	25.22±1.03	25.47±2.21	25.69±1.09	26.36±1.59
LVW/BW(mg/g)	3.22±0.04	3.13±0.06	4.43±0.03	4.19±0.01
HW/BW(mg/g)	4.65±0.10	4.37±0.08	6.17±0.24 <sup>#</sup>	6.77±0.44 <sup>*,#</sup>
LW/BW(mg/g)	4.25±0.08	4.34±0.09	6.31±0.23 <sup>#</sup>	7.34±0.42 <sup>*,#</sup>

398 LVESD, Left ventricular end-systolic dimension; LVEDD, Left ventricular end-diastolic  
399 dimension; LVESV, Left ventricular end-systolic volume; LVEDV, Left ventricular  
400 end-diastolic volume; FS, Fractional Shortening; SV, Stroke volume; CO, Cardiac output; HR,  
401 Heart rate. B W, Body weight; LVW, Left ventricular weight; HW, Heart weight; LW, Lung  
402 weight. \**P* < 0.05 vs EP3<sup>F/F</sup>, #*P* < 0.05 vs Sham, n=9-13.

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**Supplementary Table 2. Effect of Mo/Mp Ep3 deletion on cardiac function in mice challenged with dobutamine.**

	Baseline		dobutamine	
	<sup>F/F</sup> EP3	<sup>F/F</sup> Ep3 ; <sup>Cre</sup> LysM	<sup>F/F</sup> Ep3	<sup>F/F</sup> Ep3 ; <sup>Cre</sup> LysM
LVESD(mm)	2.65±0.21	2.62±0.11	1.33±0.20 <sup>#</sup>	1.46±0.13 <sup>#</sup>
LVEDD(mm)	3.52±0.27	3.63±0.19	3.38±0.13 <sup>#</sup>	3.31±0.67 <sup>#</sup>
LVESV(μl)	33.35±4.84	27.84±2.04	12.58±0.67 <sup>#</sup>	12.89±17.96 <sup>#</sup>
LVEDV(μl)	64.44±4.49	63.86±4.13	47.22±2.57 <sup>#</sup>	45.13±3.42 <sup>#</sup>
EF(%)	64.23±5.60	65.64±2.67	87.51±3.40 <sup>#</sup>	85.40±2.13 <sup>#</sup>
FS(%)	35.15±4.17	35.60±1.96	58.51±5.15 <sup>#</sup>	54.25±2.65 <sup>#</sup>
SV(%)	32.53±3.89	37.11±3.15	34.09±2.97	35.73±2.36
CO(ml/min)	14.22±1.72	15.78±1.36	18.17±1.13 <sup>#</sup>	17.25±1.15 <sup>#</sup>
HR(BPM)	401.79±7.14	400±10.81	479.94±4.94 <sup>#</sup>	487.13±7.29 <sup>#</sup>

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<sup>#</sup>*P* < 0.05 vs baseline. n=6-7.

426 **Supplementary Table 3. Histological analysis of infarcted hearts from EP3<sup>F/F</sup>Lys<sup>Cre</sup> and**  
 427 **EP3<sup>F/F</sup> mice at day 14 after MI.**  
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	EP3 <sup>F/F</sup> (n)	Ep3 <sup>F/F</sup> ;Lys <sup>Cre</sup> (n)
Total Mo/Mps (×10 <sup>4</sup> /heart)	9.45±0.91(6)	5.67±0.51*(6)
Ly6C <sup>high</sup> (×10 <sup>4</sup> /heart)	1.22±0.19(6)	0.89±0.12(6)
Ly6C <sup>low</sup> (×10 <sup>4</sup> /heart)	8.23±0.51(6)	4.79±0.58*(6)
Angiogenesis (CD31 <sup>+</sup> PCNA <sup>+</sup> cells/field)	15.52±1.53(7)	7.01±0.49*(7)
Fibrosis (Collagen % scar area)	53.46±1.94(6)	40.51±0.57*(6)
Myofibroblast (SMA <sup>+</sup> area %)	9.68±0.36(6)	5.92±0.40*(6)
Infarct area(%)	29.91±1.81(5)	44.87±3.52*(5)
EF(%)	30.00±4.19(13)	14.18±2.30*(11)

429 \* P<0.05 vs EP3<sup>F/F</sup>.

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**Supplementary Table 4. Effect of BTM on cardiac function of Ep3 KO mice after MI**

	WT→WT	WT→KO	KO→WT	KO→KO
LVEDD(mm)	3.98±0.12	4.01±0.1	4.99±0.42*	4.91±0.28*. <sup>#</sup>
LVEDD(mm)	4.55±0.1	4.79±0.13	5.32±0.37*	5.29±0.16*. <sup>#</sup>
LVESV(μl)	70.88±5.19	81.24±4.51	122.84±14.96*	122.81±9.40*. <sup>#</sup>
LVEDV(μl)	95.61±5.55	108.16±6.48	141.43±16.86*	138.8±7.35*. <sup>#</sup>
FS(%)	12.58±1.43	11.36±0.88	6.14±0.64*	6.72±0.69*. <sup>#</sup>
SV(%)	25.60±2.98	26.91±2.94	18.59±2.56*	15.88±0.85*. <sup>#</sup>
CO(ml/min)	10.88±1.06	10.86±1.47	7.90±1.28*	6.46±0.41*. <sup>#</sup>
HR(BPM)	408.50±13.45	428±10.03	419±6.76	396±3.03

\* $P < 0.05$  vs WT → WT mice, <sup>#</sup> $P < 0.05$  vs WT → KO mice, n=8-11.

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474 **Supplementary Table 5. Effect of TGFβ1 blocker SB525334 on cardiac function of**  
 475 **Mp-Ep3Tg mice after MI.**

	Control			SB525334		
	WT	Mp-EP3Tg-C	Mp-EP3Tg-E	WT	Mp-EP3Tg-C	Mp-EP3Tg-E
LVESD(mm)	4.41±0.22	3.63±0.38*	3.23±0.23*	4.65±0.49* <sup>#</sup>	5.13±0.23* <sup>#</sup>	5.02±0.32* <sup>#</sup>
LVEDD(mm)	4.95±0.29	4.50±0.29*	4.07±0.17*	4.98±0.47* <sup>#</sup>	5.52±0.21* <sup>#</sup>	5.34±0.27* <sup>#</sup>
LVESV(μl)	94.18±10.27	62.37±13.65*	43.40±6.06*	109.35±28.35* <sup>#</sup>	128.8±12.23* <sup>#</sup>	123.61±17.43* <sup>#</sup>
LVEDV(μl)	119.3±9.03	96.62±14.71*	74.08±6.70*	125.89±29.31* <sup>#</sup>	151.8±12.74* <sup>#</sup>	140.89±15.83* <sup>#</sup>
FS(%)	11.69±1.54	20.82±4.41*	21.33±2.57*	7.11±1.29* <sup>#</sup>	7.4±0.81* <sup>#</sup>	6.41±1.33* <sup>#</sup>
SV(%)	25.10±2.04	34.25±3.03*	30.67±1.04	16.55±2.02* <sup>#</sup>	22.09±1.72* <sup>#</sup>	17.29±2.08* <sup>#</sup>
CO(ml/min)	11.34±1.83	14.52±2.64*	16.35±2.45*	7.78±2.34 <sup>#</sup>	9.09±1.18 <sup>#</sup>	8.11±2.47 <sup>#</sup>
HR(BPM)	484.4±33.52	441.2±14.11	453.24±19.5	466.22±19.18	458.1±18.32	469.43±19.58

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477 \**P* < 0.05 vs WT mice, <sup>#</sup>*P* < 0.01 vs Control, n=7-8.

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498 **Supplementary Table 6. Primers for real-time PCR analysis in mice**

499	Gene	Sense	Anti-sense
500	CCR2	ATCCACGGCATACTATCAACAT	CCAAGGCTCACCATCATCGTAG
501	CX3CR1	CCTGTTATTTGGGCGACATT	ACGCCCAGACTAATGGTGAC
502	EP1	TAACGATGGTCACGCGATGG	ATGCAGTAGTGGGCTTAGGG
503	EP2	GCTCGCCTGCAACATCAGCGTTA	AGCTCGGAGGTCCCACCTTTTCCT
504	EP3	CGCACAGCAACCTGTCAAGTA	CCCCACTAAGTCGGTGGAGC
505	EP4	GGATCATGTGTGTGGTGTCC	GCAGAACTCCGAAGAAGGA
506	IL1	TCTCAACCAATCAGCACACCCGA	GATGTAGCGGAGGCTAGAGTTGC
507	IL12	ATGGCCATGTGGGAGCTGGAGAAA	GGTGGAGCAGCAGATGTGAGTGGCT
508	IL-13	CCTGGCTCTTGCTTGCCTTGG	TCTTGTGTGATGTTGCTCA
509	MMP-9	TTTGAGTCCGGCAGACAATCC	CAACCGTCCTTGAAGAAATG
510	TNF $\alpha$	TGCCTATGTCTCAGCCTCTTCG	AGGCCATTTGGGAACTTCT
511	TGF $\beta$	TGTTAAAACCTGGCATCTGA	GTCTCTTAGGAAGTAGGT
512	VEGF	GCACATAGAGAGAATGAGCTT	CCCTCCGCTCTGAACAAGGCT
513	GAPDH	CCCTTATTGACCTCAACTACA	TGGTGAGGGGCCATCCACAGTCTTCTG

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542 **Supplementary Table 7. Primers for Chip PCR analysis**

543	Gene	Sense	Anti-sense
544	S1	AGGAAGCGGATAGAATGCAG	CATCTACCCATGTGCCAGAG
545	S2	ACACGGATGAGATTGGTTGA	TTGCCATCTGAGCTGTATCC
546	S3	TTGAAATGCAGGCTCTCTTG	GGTTTCCTGTGTGGTACCCT
547	S4	GGTCAATCAGGCACAGTCAC	TCAAGTTACGAGCGTGCAA
548	S1'	GCC AGA CTA CAC AGTGCA TA	GCT TAT CTG AGC CCT TGT CTG
549	S2'	GGATCATGTGTGTGGTGTCC	GCAGAACTTCCGAAGAAGGA
550	hS	TAAGTGGCACCTCTCTCCCT	TCTTTAGATGCTGCCACAGG
551	h S1'	GCATTCCCATTCTCAGTCC	GAAGAGTGGGACCAGTCAGT
552	h S2'	CTGGGTGGATAATCAGACTG	GCTGGTTTCTGACCTGGCTA
553	hS3'	ATGAGTCTGGGCTTGGGCTGATAG	TGATGATTCAAACCTACCCGCC
554	h S4'	CTCAGTTCCTGGCAACATCTG	TGGGAGGGAAGAGGACCTGTT
555	h S5'	AGCCATTCCCTCTTTAGCCAG	ACACTCACTACCCACACAGACAC

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586 **Supplementary Table 8. Primers for plasmids construction**

587	Gene	Sense	Anti-sense
588	S3+S4	CGTTGAGCTTGCTTGTCACAGC	CGATACAAGTTTGAGACCAGCCTAG
589	S1 '+ S2 '	GTTTAGAAGATGAACCGTAAGCCTAGGC	TCTCTCTGTTTCGCTCGCCAGCGCGCT
590	hS	GCCTGTTTGCTTACGTGCAGAC	GGATACTCAGGCTCAGGTTTGTGT
591	hS3 '-hS5 '	ACAGTGACCGTGGAGACTCAAG	GAACAAAGCTGAACCTAAGGATCT

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