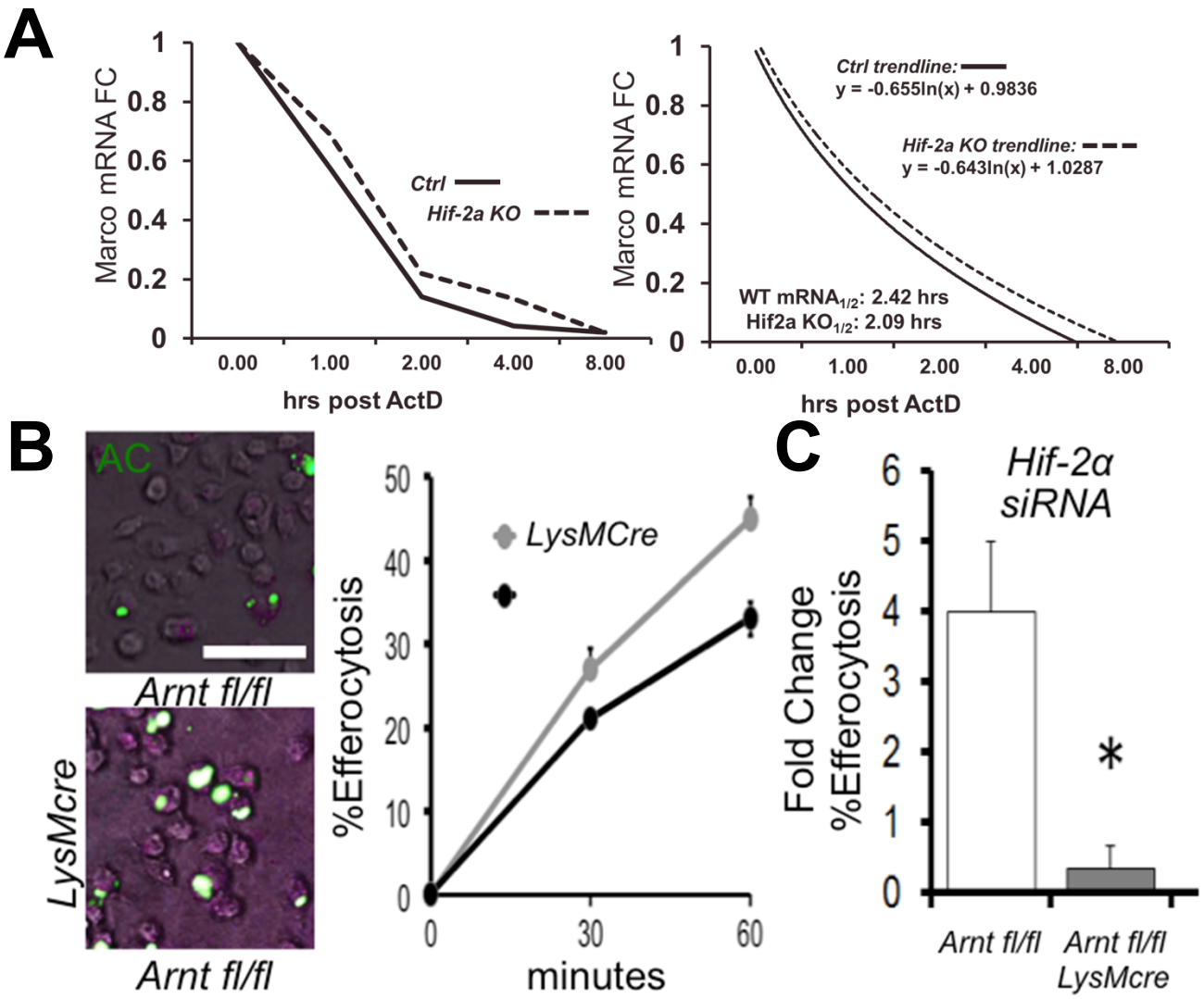
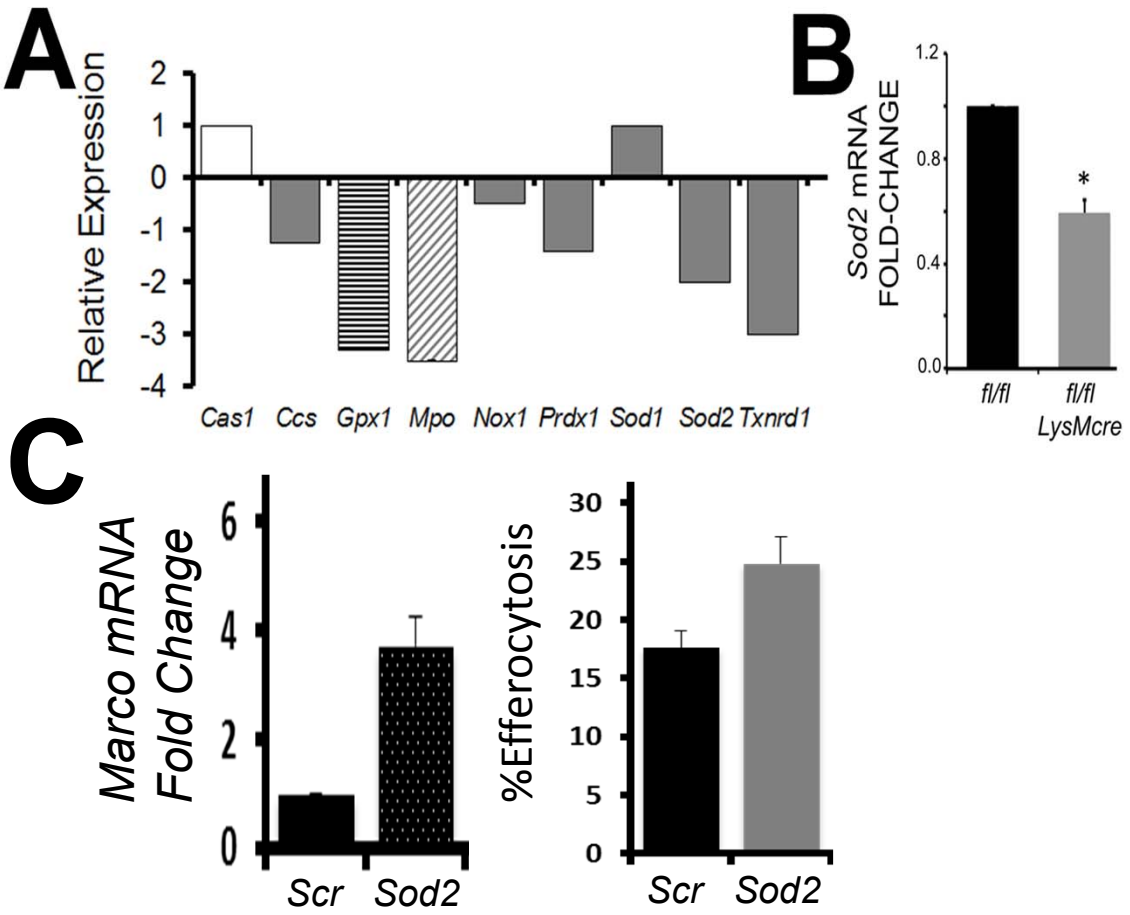
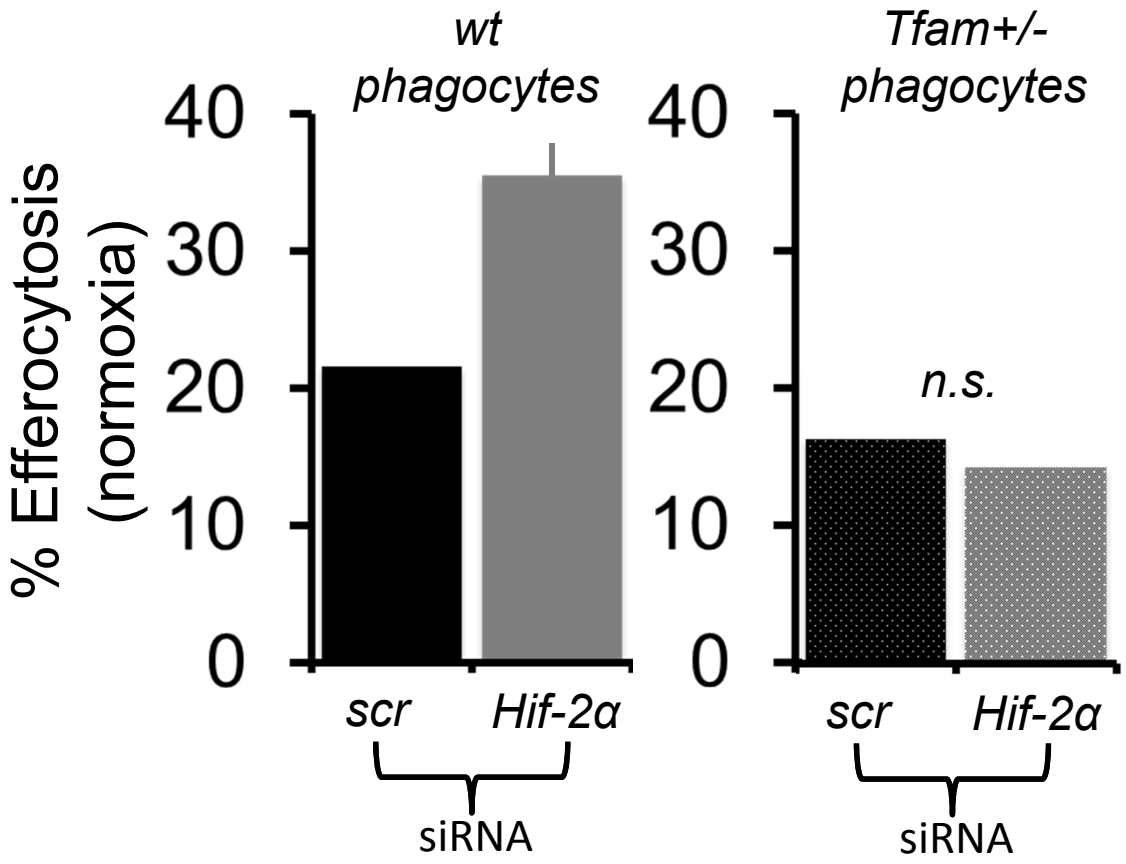


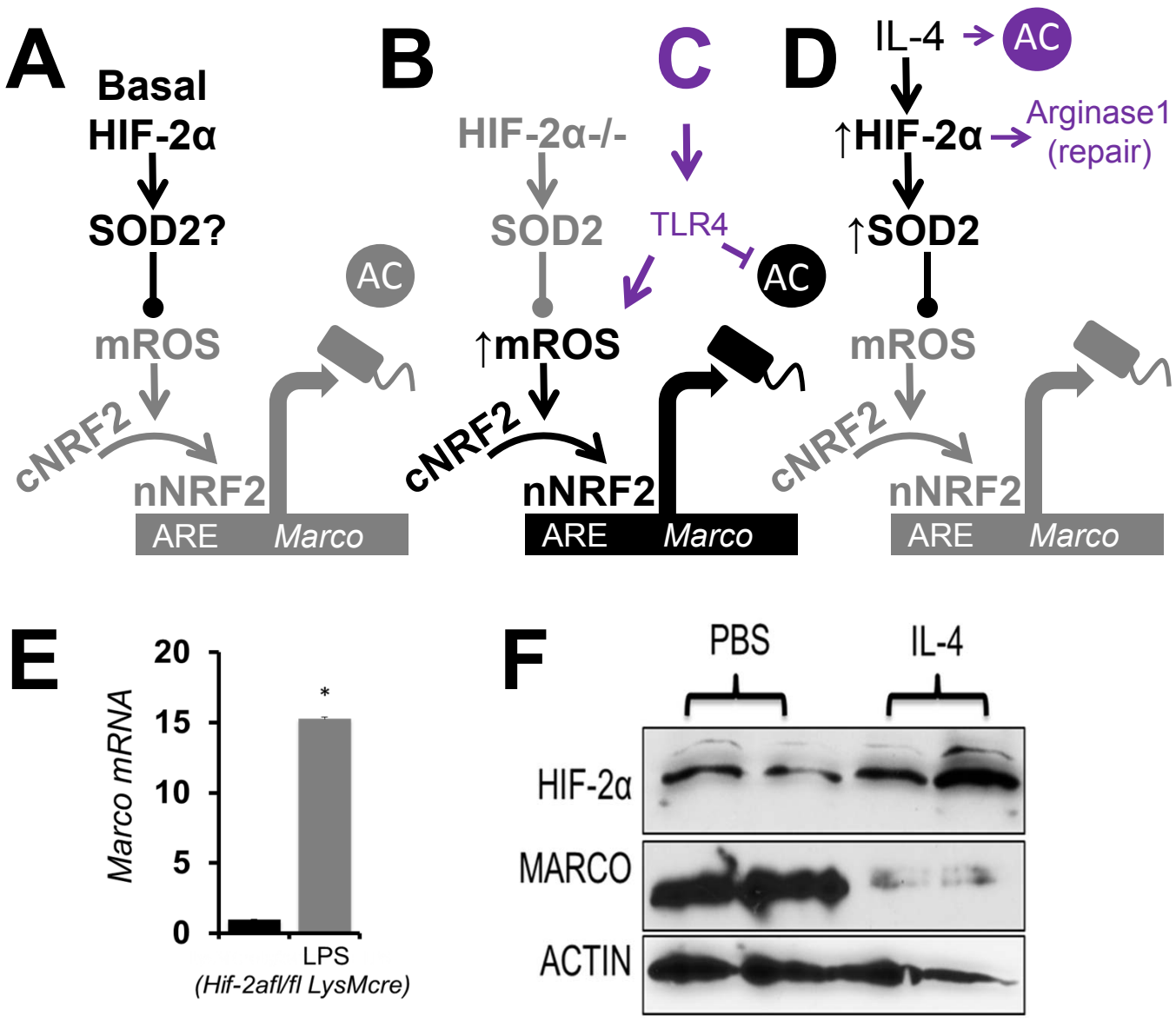

**Supplemental Figure 1. Evidence for HIF-2α transcriptional regulation of Marco Axis. (A)** Marco mRNA decay profile in the absence of *Hif-2α: Hif-2α* deficiency de-represses *Marco* transcription: MARCO mRNA from WT and Hif-2α KO cells have similar decay profiles/half-lives. For the mRNA stability assay: Control and *Hif-2αfl/fl* BMDMs were treated with 10ug/ml Actinomycin D or DRB to halt transcription and total cytoplasmic mRNA was collected 0, 1, 2, 4, and 8 hours after treatment. Relative MARCO mRNA levels were enumerated. (**B**) Enhanced efferocytosis in *Arnt fl/fl LysMcre* primary MΦs under normoxic culture conditions. Micrographs were captured after overlaying fluorescently labeled (calcein-AM) apoptotic cells (ACs) onto bone marrow derived MΦs. Scale bar is 50 micrometers. Line graph is after enumeration of % efferocytosis at indicated times post AC overlay. (**C**) Fold change in % efferocytosis after knocking down Hif-2α with siRNA in *Arnt fl/fl* vs. *Arnt fl/fl LysMcre* bone marrow derived MΦs.




**Supplemental Figure 2. Antioxidants are reduced *Hif-2α*-deficient macrophages. (A)** Primary bone-marrow-derived macrophages were subjected to qPCR and gene expression compared to WT cells. *Cas1* is catalase. *Ccs* is copper chaperone for superoxide dismutase. *Gpx1* is glutathione peroxidase 1. *Mpo* is myeloperoxidase. *Nox1* is NADPH oxidase1. Prdx1 is peroxiredoxin 1. *Sod1* is superoxide dismutase 1. *Sod2* is superoxide dismutase 2. *Txnrd1* is thioredoxin reductase 1. (**B**) *Sod2* validation by qPCR. Sod-2 knockdown increases Marco and efferocytosis. **(C)** WT macrophages were treated with either scrambled (Scr) or Sod2 siRNA prior to qPCR and efferocytosis assays.




**Supplemental Figure 3. *Tfam*-deficient macrophages and efferocytosis +/- Hif-2α.** Bone marrow derived macrophages were utilized from either WT or *Tfam+/-* macrophages and treated with indicated scrambled (scr) or *Hif-2α* siRNA. Subsequently, efferocytosis was enumerated after adding fluorescently labelled apoptotic Jurkat cells.




**Supplemental Figure 4. Working Model of HIF-2α : MARCO axis in Macrophages during Steady State, Inflammation, and Repair** (**A**) Basal HIF-2α prevents MARCO induction at steady state through regulation of mROS. (**B**) In experimental Hif-2α-deficient macrophages, elevations in mROS lead to nuclear translocation of NRF2 (cNRF2>nNRF2) and NRF2-dependent transcriptional induction of Marco. (**C**) Under pathophysiological situations that induce mROS, such as after TLR4 agonism (PMID 21525932), Marco is induced yet efferocytosis is suppressed (the latter through protease-dependent cleavage of Apoptotic Cell receptors), cumulatively leading to a select pro-bacterial phagocytic mobilization of MARCO. (**D**) Conditions that induce HIF-2α, such as IL-4, polarize an M2-like macrophage response (PMID 20194441) and in turn suppress Marco induction and de-emphasize bacterial clearance. **(E)** Following LPS treatment, MARCO transcription is induced, even in the absence of HIF-2α. Primary bone marrow derived macrophages were treated with LPS and *Marco* mRNA measured by qPCR in *Hif-2αfl/fl* LysMcre macrophages. **(F)** *In vitro* IL-4 treatment of Mϕs. IL-4 elevates HIF-2α protein, and reduces MARCO, in isolated primary Mϕs. Bone marrow-derived Mϕs were treated with 100ng IL-4 vs PBS and immunoblotted for indicated proteins.