Current treatments for fibrotic diseases include modulating the immune response by inhibiting macrophage function. While over-active macrophages can lead to increased production of collagen and other scar-forming molecules, research has shown that these cells are also essential for tissue regeneration. In this study, we use a recently developed model of mammalian tissue regeneration, the African spiny mouse (*Acomys cahirinus*) to investigate macrophage activity during regeneration. We hypothesized that unique macrophage activity in *Acomys* promotes regeneration over scar formation. To test this hypothesis, we isolated bone marrow derived macrophages (BMDM) and stimulated macrophage maturation to an M1 (classically activated) or M2 (alternatively activated) phenotype *in vitro*. Previous studies in *Mus* have demonstrated that M1 macrophages produce high levels of *Cd86* and *Socs3* whereas M2 macrophages produce high levels of *Cd206* and *Tgf1*. Using these macrophages from both species we quantified phenotypic differences in gene expression. First, we observed that *Acomys* failed to upregulate *Cd86* across all phenotypes, suggesting this *Mus* M1 markers is not conserved across species. Instead, we found that *Socs3* was strongly upregulated after M1 stimulation supporting this as a cross-species marker for classical stimulation. Next, we observed that macrophages from both species responded similarly to M2 stimulation based on upregulation of *Cd206* and *Tgf1.*  Lastly, we found that macrophages from both species express *collagen 1* and low levels of *fibronectin.* Together, our results suggest that macrophages from different species can respond differently to specific external cues and may directly contribute to matrix production.