Monocytes serve as a central defense system against infection and injury but can also promote pathological inflammatory responses. Considering the evidence that monocytes exist in at least two subsets committed to divergent functions, we investigated whether distinct factors regulate the balance between monocyte subset responses in vivo. We identified a microRNA (miRNA), miR-146a, which is differentially regulated both in mouse (Ly-6C(hi)/Ly-6C(lo)) and human (CD14(hi)/CD14(lo)CD16(+)) monocyte subsets. The single miRNA controlled the amplitude of the Ly-6C(hi) monocyte response during inflammatory challenge whereas it did not affect Ly-6C(lo) cells. miR-146a-mediated regulation was cell-intrinsic and depended on Relb, a member of the noncanonical NF-κB/Rel family, which we identified as a direct miR-146a target. These observations not only provide mechanistic insights into the molecular events that regulate responses mediated by committed monocyte precursor populations but also identify targets for manipulating Ly-6C(hi) monocyte responses while sparing Ly-6C(lo) monocyte activity.