***Supplementary Material: Video of redoxosomal signaling for IL-1β.** (*Step 1*) In the resting state, the cell expresses Nox, an anion channel(s) (AC), and IL-1R1 on the plasma membrane. Following IL-1β binding, early effectors including MyD88 are recruited to the receptor at the plasma membrane and initiate endocytosis. (*Step 2*) Rac1 recruits Nox into the early endosome by tethering (indirectly or directly) the receptor with the Nox complex. It remains unclear how anion channel(s) are recruited into the endosome. (*Step 3*) Phox subunits (p47phox and p67phox in the case of Nox2) recruit to the Nox complex in the newly formed endosomes. This may be facilitated by changes in inositol phospholipids in the endosomal membrane (not shown). To maintain Rac1 in a GTP-bound active state, SOD1 is recruited to Rac1. In the movie, the SOD binding event is shown to occur following endocytosis, but it is still unclear at what point SOD1 recruits to Rac1. The activated Nox complex (*blue protein complex*) transfers an electron from NADPH to molecular oxygen (*blue molecules*) to produce membrane impermeable superoxide (*red molecules*) in the lumen of the redoxosome. The superoxide may spontaneously dismutate to hydrogen peroxide (*yellow molecules*), which can pass through the endosomal membrane and out of the redoxosome (not shown). Alternatively as shown in the movie, a DIDS/NFA-sensitive chloride channel may transport the superoxide outside of the redoxosome, where it is subsequently converted to hydrogen peroxide. (*Step 4*) The localized production of hydrogen peroxide at the surface of redoxosomes transmits redox-specific signals to either the receptor or one of the downstream effectors IRAK or TRAF6 (as shown in movie), allowing for docking of the IRAK/TRAF6 effector complex and subsequent activation of pathway-specific IKKKs. (*Step 5*) Activation of NFκB is then initiated through the action of IKKK-mediated phosphorylation of the IKK complex, which leads phosphorylation of the IκB complex and mobilization NFκB to the nucleus (not shown). (*Step 6*) The redoxosomal-signaling pathway is downregulated as the buildup of cytosolic hydrogen peroxide oxidizes Rac1 on the surface of the endosome, resulting in the disassociation of SOD1 from Rac1. In the absence of SOD1 binding to Rac1, Rac1 quickly hydrolyzes GTP and becomes inactive, leading to the termination of Nox generated superoxide production. This movie is based on findings from refs. 42, 68, 78, and 83.