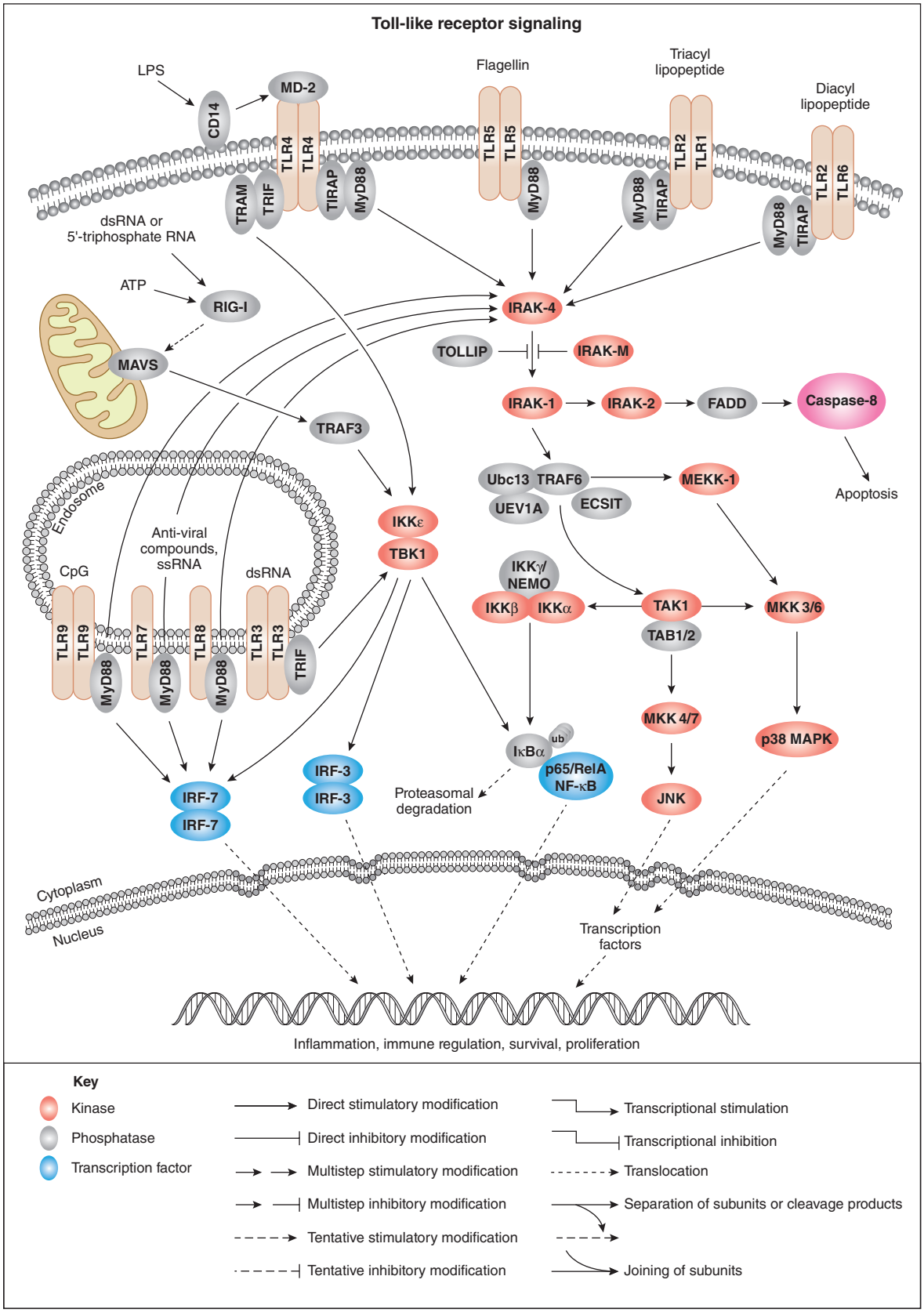

FIGURE 145e-3 **Cellular signaling pathways for production of inflammatory cytokines in response to microbial products.** Microbial cell-surface constituents interact with Toll-like receptors (TLRs), in some cases requiring additional factors such as MD-2, which facilitates the response to lipopolysaccharide (LPS) via TLR4. Although these constituents are depicted as interacting with the TLRs on the cell surface, TLRs contain extracellular leucine-rich domains that become localized to the lumen of the phagosome upon uptake of bacterial cells. The internalized TLRs can bind to microbial products. The TLRs are oligomerized, usually forming homodimers, and then bind to the general adapter protein MyD88 via the C-terminal Toll/IL-1R (TIR) domains, which also bind to TIRAP (TIR domain-containing adapter protein), a molecule that participates in the transduction of signals from TLRs 1, 2, 4, and 6. The MyD88/TIRAP complex activates signal-transducing molecules such as IRAK-4 (IL-1Rc-associated kinase 4), which in turn activates IRAK-1. This activation can be blocked by IRAK-M and Toll-interacting protein (TOLLIP). IRAK-1 activates TRAF6 (tumor necrosis factor receptor–associated factor 6), TAK1 (transforming growth factor β–activating kinase 1), and TAB1/2