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The cross talk between NK cells and macrophages is emerging as a major line of defense against microbial infections and tumors. This study reveals a complex network of soluble mediators and cell-to-cell interactions allowing human classically activated (M1) macrophages, but not resting (M0) or alternatively activated (M2) macrophages, to prime resting autologous NK cells. In this article, we show that M1 increase NK cell cytotoxicity by IL-23 and IFN-β-dependent upregulation of NKG2D, IL-1β-dependent upregulation of NKp44, and trans-presentation of IL-15. Moreover, both IFN-β-dependent cis-presentation of IL-15 on NK cells and engagement of the 2B4-CD48 pathway are used by M1 to trigger NK cell production of IFN-γ. The disclosure of these synergic cellular mechanisms regulating the M1-NK cell cross talk provides novel insights to better understand the role of innate immune responses in the physiopathology of tumor biology and microbial infections.