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## **Activating NK cell receptors providing immunity against viruses and tumors**

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### **Abstract**

NK cells use activating receptors employing three biochemically distinct pathways in order to provide innate immunity against tumors and pathogens. Similar to the B- and T-cell receptors, several NK cell receptors, including the activating KIR and Ly49 receptors, signal by association with the ITAM-bearing adapter protein DAP12. Ly49H has been implicated directly in viral recognition. ITAM-based signaling requires the Syk and ZAP70 kinases and the involvement of this pathway in tumor killing is under study. A second pathway of NK activation involves PI3 kinase. DAP10 adapter protein activates this pathway and permits NK cells to kill tumors bearing ligands of the DAP10-associated NKG2D receptor. Studies using neutralizing anti-NKG2D mAb *in vivo* implicate this receptor in both anti-tumor and anti-viral functions. An independent pathway of activation which amplifies these responses involves the SAP adaptor protein linked to the CD244 (2B4) NK receptors. Full NK activation requires a synergy between the PI3 kinase, Syk/ZAP70 and SAP pathways to permit optimal attack against cancer.

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