5 Summary

The receptor TIM-3 has emerged as an important regulator of innate immune responses. However, whether TIM-3-induced signaling promotes or inhibits the activation and maturation of dendritic cells (DCs) still remains uncertain. Additionally, the TIM-3 signaling events involved in this immunoregulatory function are yet to be established. Here we report that TIM-3 crosslinking by anti-TIM-3 Ab inhibited DC activation and maturation by blocking the NF-κB pathway. After Ab-mediated crosslinking, TIM-3 became tyrosine-phosphorylated, which then sequentially bound and activated the nonreceptor tyrosine kinases Bruton's tyrosine kinase (Btk) and c-Src. Activation of Btk-c-Src signaling in turn triggered the secretion of some inhibitory factor(s) from DCs that inhibited the NF-κB pathway and subsequent activation and maturation of DCs. Silencing of Btk or c-Src abrogated the inhibitory effects of TIM-3 on DCs. These results demonstrate an essential role for Btk-c-Src signaling in TIM-3-induced DC suppression. Thus, in addition to demonstrating an inhibitory role for TIM-3 signaling in DC activation, we define the molecular mechanism by which TIM-3 mediates this effect (Fig. 5.1).

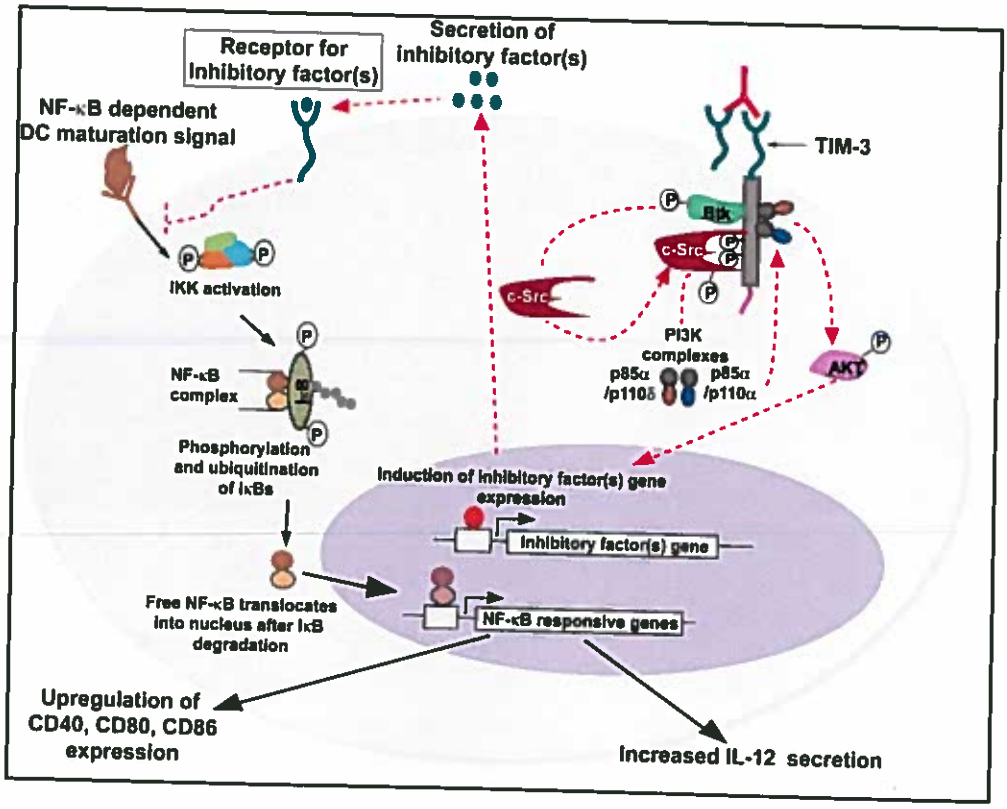

Fig. 5.1 Model depicting the molecular mechanism of TIM-3-mediated immunoregulation of DCs