Mast cells play a key role in host defense against lethal herpes simplex virus infection through TNF–α and IL–6 production induced by keratinocyte–derived alarmin IL–33

The essential contribution of mast cells (MCs) to bacterial host defense has been well established; however, little is known about their role in viral infections in vivo. Here, we found that intradermal injection with HSV–2 into MC deficient KitW–/– mice lead to increased clinical severity and mortality with elevated virus titers in HSV–infected skins. Ex vivo HSV–specific tetramer staining assay demonstrated that MC deficiency did not affect the frequency of HSV–specific CTLs in draining lymph nodes. Moreover, the high mortality in KitW–/– mice was completely reversed by intradermal reconstitution with BMMCs from wild–type, but not TNF–α/– or IL–6/–, mice. HSV did not directly induce TNF–α or IL–6 production by BMMCs, whereas supernatants from HSV–infected keratinocytes induced production of these cytokines by BMMCs without degranulation. Furthermore, IL–33 expression was induced in HSV–infected keratinocytes and blocking the IL–33 receptor, T1/ST2 on BMMCs significantly reduced TNF–α and IL–6 production by BMMCs. These results indicate MC involvement in host defense at HSV–infected sites through TNF–α and IL–6 production, which is induced by keratinocyte–derived IL–33.