Abstract

Endoplasmic reticulum (ER) stress serves as a key modulator of the inflammatory response by controlling nuclear factor-kappaB (NF-κB) signaling. Previous studies from our laboratory have reported an abnormal induction of ER stress linked to progesterone resistance in human endometriotic cells. Therefore, an aberrant ER stress response to progesterone might contribute to the altered inflammatory response observed in endometriotic tissues. To evaluate this hypothesis, we investigated whether ER stress is involved in regulation of NF-κB in endometrial stromal cells and whether induction of aberrant ER stress in endometriotic stromal cells affects pro-inflammatory cytokine production. We found that tunicamycin-induced ER stress inhibited NF-κB activation and pro-inflammatory cytokine (IL-6 and COX2) production in TNF-α- or IL-1β-treated normal endometrial stromal cells (NECSs). Tunicamycin increased the expression of A20 and C/EBPβ, which are negative regulators of NF-κB, and this increase inhibited NF-κB activity in NESCs incubated with TNF-α- or IL-1β. Similarly, progesterone increased A20 and C/EBPβ expression through upregulation of ER stress in NESCs, resulting in inhibition of NF-κB activity and IL-6 and COX2 production. However, progesterone had no significant effects on induction of ER stress, A20 or C/EBPβ expression, NF-κB activity, or IL-6 or COX2 production in ovarian endometriotic cyst stromal cells (ECSCs). In contrast, upregulation of ER stress by tunicamycin significantly reduced IL-6 and COX2 production by inhibiting NF-κB activity in ECSCs. In conclusion, our results suggest that NF-κB activity in endometriotic stromal cells was not inhibited because of an aberrant ER stress response to progesterone, resulting in an increase in pro-inflammatory cytokine production.