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AMP-activated protein kinase stimulates ADAM10 activity in human aortic endothelial cells by triggering its translocation to the cell surface

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Objectives: Recently, we have shown that extracellular Ca^{2+} influx-dependent adenosine monophosphate-activated protein kinase (AMPK) activation induces a disintegrin and metalloprotease 10 (ADAM10) translocation to the cell surface, where it acts as a sheddase. Independently of Ca^{2+} influx, AMPK can be activated by 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR) through different mechanisms. In this study, we investigated whether Ca^{2+} influx-independent AMPK activation also stimulates ADAM10 activity.

Methods: Human aortic endothelial cells (HAECs) were cultured. Protein abundance was assessed by Western blot analysis. ADAM10 on the cell surface was visualized by immunofluorescence staining.

Results: Upon treatment with AICAR, AMPK was rapidly activated, which in turn induced translocation of ADAM10 to the cell surface and ectodomain shedding of the receptor for advanced glycation end products (RAGE). Inhibition of ADAM10 with compound C, GI 254023X or depletion of ADAM10 by siRNA transfection prevented AICAR-induced ectodomain shedding of RAGE (Figure 1). In addition, inhibition of AMPK with compound C, GI254023X or siRNA-mediated depletion of AMPK prevented AICAR-induced ADAM10 translocation to the cell surface and ectodomain shedding of RAGE (Figure 2).

Conclusions: AMPK activation unrelated to extracellular Ca^{2+} influx also triggers ADAM10 translocation to the cell surface, and thereby causes ADAM10-mediated ectodomain shedding of RAGE. Because ADAM10 is able to cleave the ectodomain of cell surface receptors of various inflammatory mediators, it can be a new mechanism of anti-inflammatory effects of AMPK.

Figure 1. AMPK inhibition prevented AICAR-induced ectodomain shedding of RAGE