Cold exposure-induced asthma exacerbation through airway epithelial barrier disruption in mice

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Abstract

Background: Cold exposure can trigger asthma attacks. However, the underlying mechanism is yet to be elucidated. We hypothesize that low temperature reduces occludin expression and compromises airway epithelial barrier function, which, in turn, results in asthma exacerbation. **Methods:** We examined occludin expression in Beas-2B cells exposed to either 29 °C or 37 °C. The following drugs were administered prior to cold treatment: MG132 (a proteasome inhibitor), cycloheximide (a protein synthesis inhibitor), HC-067047 plus GSK2193874 (transient receptor potential vanilloid 4 [TRPV4] antagonists), or C4-ceramide (an SGK1 activator). siNedd4-2 was transfected into Beas-2B cells to investigate the role of Nedd4-2 in mediating cold-induced occludin instability. In animal experiments, we treated ovalbumin (OVA)-induced asthmatic mice with either a thermoneutral temperature of 30 °C or repeated cold stress (10 °C, 6 h/day) for 2 weeks. Either GSK2193874 or C4-ceramide was administered during the cold treatment. After a final OVA challenge, pulmonary permeability, serum IgE levels, and lung inflammation were assessed. **Results:** Treatment at 29 °C for 1-9 h significantly reduced Beas-2B cell occludin expression, which was rescued upon treatment with MG132, HC-067047 plus GSK2193874, C4-ceramide, or the Nedd4-2 knockdown. Notably, low temperatures affected occludin stability through SGK1/Nedd4-2-dependent proteolysis. *In vivo* analyses revealed that repeated cold exposure compromised the airway epithelial barrier function and exacerbated lung inflammation in mice, which was partially attenuated by the GSK2193874 or C4-ceramide injection. **Conclusions:** We identified a new mechanism underlying cold-induced asthma exacerbation that may involve SGK1/Nedd4-2-mediated occludin proteolysis, resulting in epithelial barrier dysfunction.

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Running title: *Cold-induced epithelial dysfunction in asthma*

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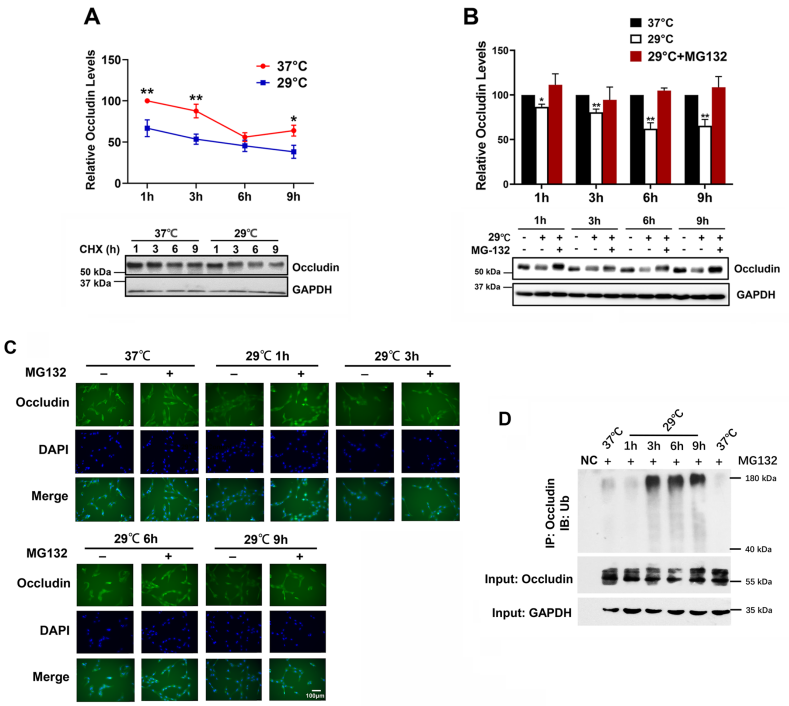
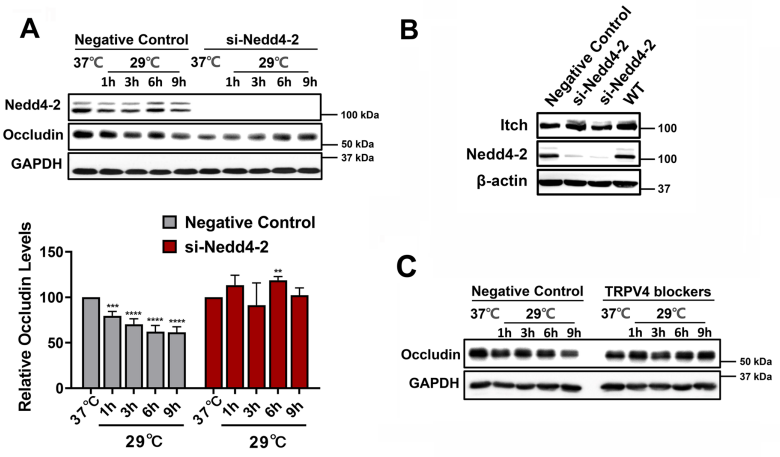


Figure 2_Zhou et al.



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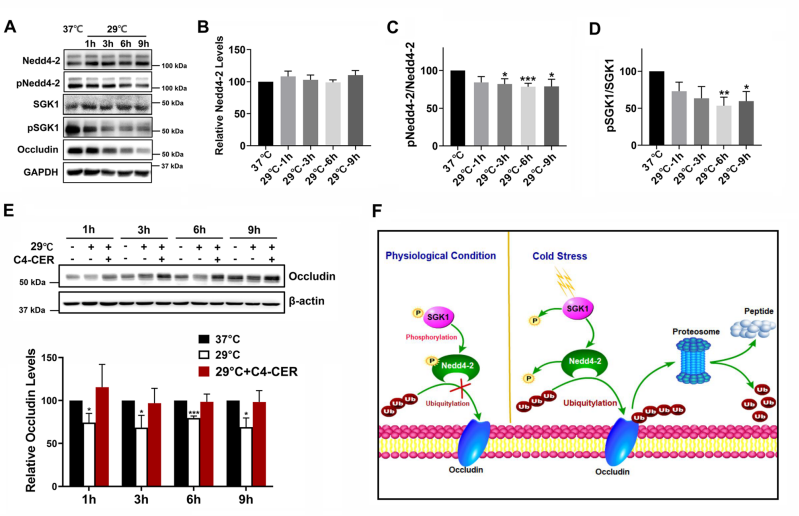

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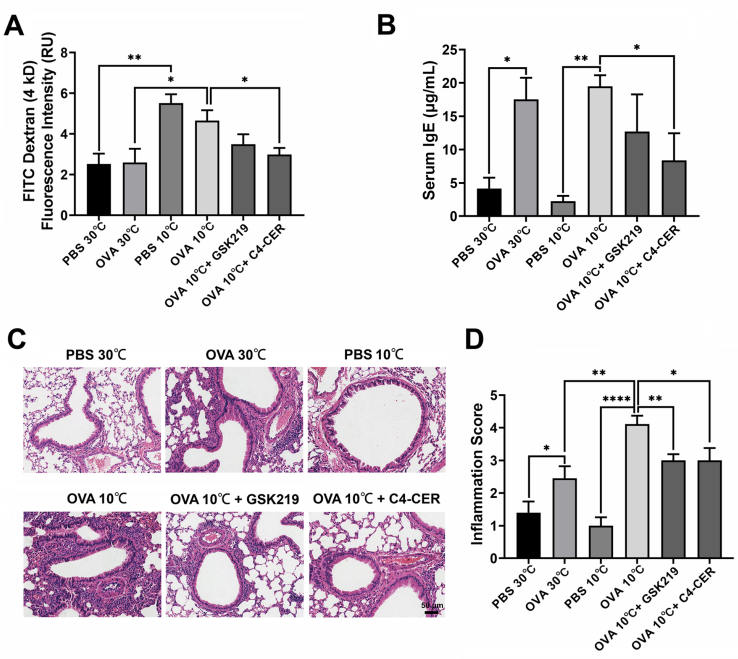

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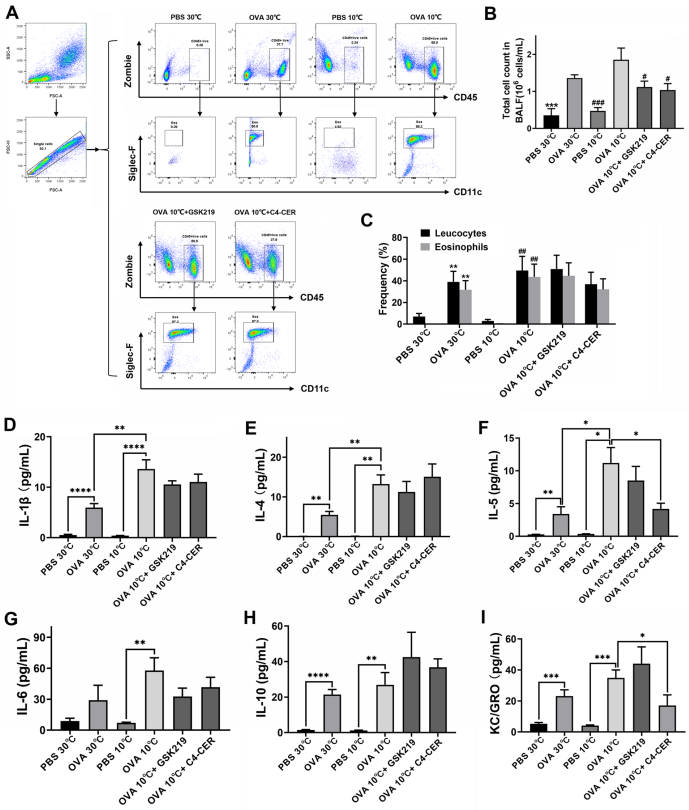

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