



**Figure S1. Hypothetical signal transduction pathway that involves PAR2 and TRPM8 in cold stimulation based on the reported pathway.** After TRPM8 is activated by cold stimulation, Ca<sup>2+</sup> that has entered the cell via TRPM8 (a) activates PLCδ4 (b). PLC hydrolyzes PIP2 to IP3 and DAG (c). TRPM8 requires PIP2 for its activity (d). During PAR2 activation, the G<sub>αq</sub> subunit stimulates PLCβ (e) and causes a decrease in PIP2 levels (c), which could impair TRPM8 channel activity. At the same time, the G<sub>αq</sub> subunit which may be activated by PAR2 binds directly to the TRPM8 channel to impair channel activity (f). IP3 mobilizes Ca<sup>2+</sup> stores from the endoplasmic reticulum (g) and increases intracellular Ca<sup>2+</sup> concentrations. DAG or high Ca<sup>2+</sup> levels further activate PKC (h) to inhibit TRPM8 (i). In carriers of the A allele of the rs2243057 SNP of *PAR2*, PAR2 expression is higher and PIP2 levels would be lower through PLC activation, possibly resulting in the stronger inhibition of TRPM8 activity. C allele carriers of the rs12992084 SNP of *TRPM8* may speculatively have low TRPM8 expression. However, further direct evidence is needed to confirm this hypothesis.

Terms enclosed by rectangles: protein. Terms enclosed by circles: molecule. Red arrows: activate. Blue arrows: inhibit. Dotted line arrows: release. Question mark: a speculation. PAR2, protease activated receptor 2; TRPM8, transient receptor potential melastatin 8; GPCR, G protein-coupled receptor; G<sub>αq</sub>, G-protein α<sub>q</sub> subunit; PIP2, phosphatidylinositol 4,5-bisphosphate; PLC, phospholipase C; IP3, inositol trisphosphate; DAG, diacylglycerol; PKC, phosphokinase C; ER, endoplasmic reticulum; PM, plasma membrane.