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# Prostaglandin (PG) $E_2$-EP2 signaling induces intracranial aneurysm through an amplifying loop via NF-κB.

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**Abstract**

Intracranial aneurysm (IA) is a cerebrovascular disease with a high prevalence and sometimes accompanied by life-threatening subarachnoid hemorrhage after rupture. In a rodent IA model, we have revealed a critical role for chronic inflammation mediated by NF-κB activation and macrophage infiltration through monocyte chemoattractant protein-1 (MCP-1) expression. However, how the inflammation becomes chronic in the process of IA formation remains unknown. Here we show that prostaglandin (PG) $E_2$, a lipid mediator related to inflammation, and its receptor EP2 are critical for IA formation. Enzymes for $PGE_2$ synthesis, such as COX-2 and mPGES-1, were up-regulated in IA walls. Consistently, rats treated with a COX-2 inhibitor exhibited a lower incidence of IA formation with less accumulation of macrophages. EP2-deficient mice failed to show IA formation, suggesting a role for EP2 in this process. In primary endothelial cells from human carotid artery, laminar shear stress, a most likely trigger for IA formation proposed from previous studies of flow dynamics, induced COX-2 and EP2 expression, suggesting up-regulated $PGE_2$-EP2 signaling. Further, EP2 stimulation activated NF-κB in these cells, suggesting that $PGE_2$ signaling regulated NF-κB activation. Importantly, a deficit in $PGE_2$-EP2 signaling abolishes NF-κB activation in IA walls and vice versa. Therefore, we propose that a positive feedback loop through COX-2-$PGE_2$-EP2-NF-kB signaling contributes to chronic inflammation associated with IA.