PGE_2-EP4 signaling induces blood flow recovery via accumulation of Tregs.

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Prostaglandin E_2 (PGE_2) is pro-inflammatory and immunomodulatory lipid mediator formed from PGH2 by microsomal Prostaglandin E Synthase-1 (mPGES-1). PGE_2 binds EP receptors, EP1-EP4, and induces pharmacological function. We analyzed what type of EP receptor is most important for recovery from ischemia.
Method) Male 6-8 weeks old C57Bl/6N (wild type=WT), EP4WT and EP4 receptor deficient mice (EP4KO) were used. Ischemic hind limb model was made by femoral artery ligation. Blood flow recovery was estimated by leaser Doppler images. Angiogenesis was estimated by expression of CD31, TGF-beta and SDF-1 by using immunohistichemical analysis and real time PCR. Contribution of regulatory T cells (Tregs) was estimated by immunohistochemical study and real time PCR against FOXP3 expression, that was specific transcript factor for Tregs.
Results) Expression of EP4 receptor in the ischemic muscle was enhanced compared to other EP receptors. Selective EP4 antagonist significantly suppressed recovery from ischemia compared to vehicle treated mice. Furthermore, blood flow recovery was significantly suppressed in EP4KO compared to EP4WT. Sixty seven percentage of EP4KO showed necrosis in ligated foot in contrast, no necrosis lesion was seen in EP4WT. The number of accumulated $FOXP3^+$ cells in the ischemic muscle was decreased in EP4KO compared to WT. Expression of TGF-beta and SDF-1 were suppressed in EP4KO. Moreover, EP4KO transplanted with WT-Tregs ($CD4^+CD25^+$) significantly enhanced blood flow recovery compared to EP4KO transplanted with non-Tregs ($CD4^-CD25^+$).
Those results suggested that PGE_2-EP4 signaling induced recovery from ischemia via accumulating Tregs. Highly selective EP4 agonist might be useful for treating peripheral artery disease.