Myosin IIa is critical for cAMP-mediated endothelial secretion of von Willebrand factor

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Luo JinCai (罗金才) at the Laboratory of Vascular Biology, Institute of Molecular Medicine, Peking University, recently reported that Myosin IIa is critical to blood homeostasis in protection of vascular injury mediated via endothelial secretion of von Willebrand factor (VWF), which was published in *Blood* (2018, 2).

Weibel-Palade bodies (WPBs), endothelium-specific secretory granules, deliver hemostatic and inflammatory mediators including VWF and P-selectin in response to a variety of agonists. In a previous study, Dr. Luo's team showed that focal adhesion protein zyxin mediates the formation of actin frameworks on exocytic WPBs before fusion. However, the detailed mechanism by which zyxin regulates the reorganization of actin filaments is still unknown.

In this report, using affinity purification and co-immunoprecipitation assay, Dr. Luo's team found that myosin IIa is the most abundant interacting protein of zyxin. Downregulation of myosin IIa by shRNA significantly suppresses both forskolin—and epinephrine-induced VWF secretion. Interestingly, in resting cells, the inhibition of myosin activity and blocking the phosphorylation of myosin IIa at S1943 decreased the peripheral localization of Rab27-positive WPBs along stress fibers. Following the stimulation with cAMP activating agents, myosin IIa interacted with zyxin and this required the phosphorylation of S1916 on myosin IIa mediated by CK2 to support the formation of functional actin framework, facilitating fusion and subsequent exocytosis (Figure). Notably, endothelial specific myosin IIa null mice displayed impaired epinephrine-stimulated VWF release, prolonged bleeding time and thrombosis. Therefore, their findings implicate myosin IIa as an important regulator of blood homeostasis under pathophysiological conditions.

Since mutations in the *MYH9* gene (myosin IIa) are linked to a number of autosomal dominant disorders including bleeding, this discovery may have important clinical implications as indicated by an editorial commentary in the same issue of *Blood*.

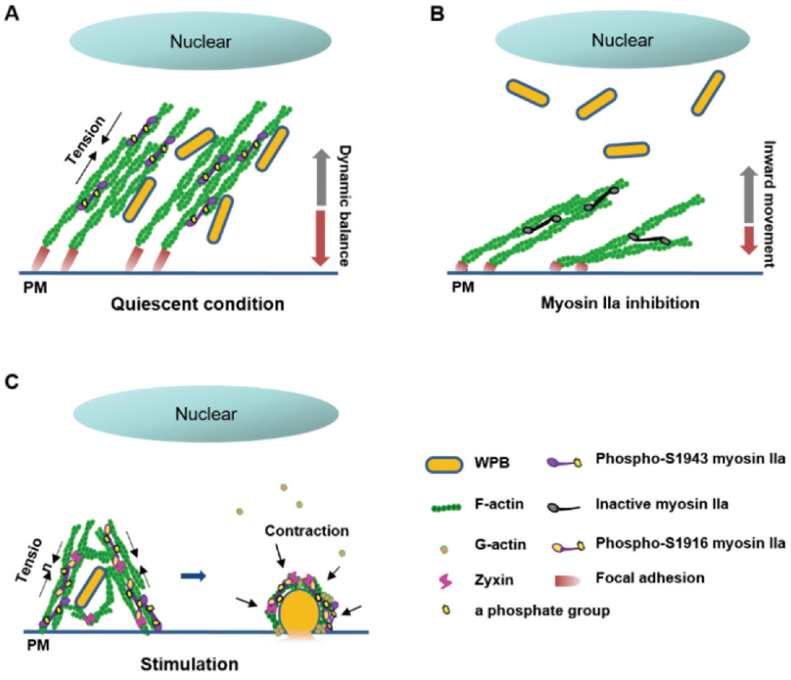

Figure A working model for the mechanism that myosin IIa couples the maintenance of mature WPB in the peripheral region to the promotion of VWF secretion in synergy with zyxin via spatiotemporally distinctive actin remodelling using different phosphorylation sites.