Force triggers YAP nuclear entry by mechanically regulating transport across nuclear pores

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YAP is a mechanosensitive transcriptional activator with a critical role in cancer, regeneration, and organ size control. Here we show that force applied to the nucleus directly drives YAP nuclear translocation by decreasing the mechanical restriction of nuclear pores to molecular transport. We demonstrate that the nucleus only connects mechanically to the cytoskeleton above a threshold in substrate rigidity, allowing forces exerted through focal adhesions to reach the nucleus. This leads to nuclear flattening, which increases YAP nuclear import by decreasing the mechanical restriction of nuclear pores to molecular transport. This restriction is further regulated by the mechanical stability of the transported protein. Control of YAP translocation by nuclear force is independent of focal adhesions, the actin cytoskeleton, substrate rigidity, cell-cell adhesion, and the Hippo pathway. Our results unveil a mechanosensing mechanism mediated directly by nuclear pores, demonstrated for YAP but with potential general applicability in transcriptional regulation.