Title: **Isthmin is a novel secreted angiogenesis inhibitor that inhibits tumor growth in mice**
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Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis. Tumors rely on blood circulation to provide oxygen and nutrients that are essential for their growth and survival. Therefore, inhibition of angiogenesis can starve tumors to death. Anti-angiogenesis is therefore a promising therapeutic approach for cancer.

Isthmin (ISM) is a gene highly conserved in vertebrates from fish to human. It is expressed in a particular region of the brain in the model organism *Xenopus* (african clawed frog) with no previously known functions. It encodes a 60 kD protein which is released to the extracellular matrix (outside of cell). Protein sequence analysis revealed that ISM contains two protein domains: a TSR domain in the central region and a hypothetical AMOP domain at the C-terminus. In this work, we demonstrate for the first time that ISM is a novel angiogenesis inhibitor. Recombinant mouse ISM generated from genetic engineering method inhibited angiogenesis in cell culture and in mouse. It mitigated blood vessel endothelial cell proliferation and also induced endothelial cell apoptosis (programmed cell death) through activation of caspases in the cell. High amount of ISM significantly suppressed mouse melanoma tumor growth through inhibition of tumor angiogenesis. In addition, suppression of isthmin gene expression in zebrafish embryos using morpholino antisense oligonucleotides led to disorganized blood vessels in the trunk. Significantly, we have identified that $\alpha v\beta 5$ integrin is a cell surface receptor for ISM.

Our results demonstrate that ISM is a novel and naturally produced angiogenesis inhibitor protein that functions in both physiological as well as tumor angiogenesis. It has the potential to be further developed into a therapeutic agent for cancer.

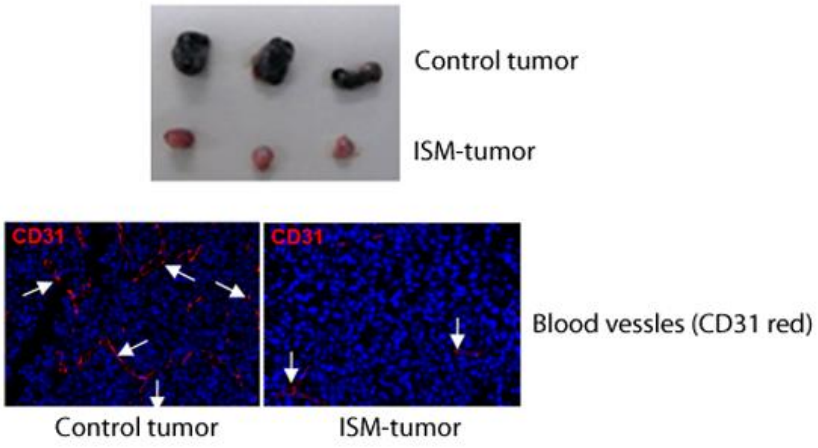

Figure. Overexpression of ISM in tumor potently suppressed tumor growth by inhibiting tumor angiogenesis.