[S2-2] [10/19/2001(Fri) 11:00-11:30 / Hall B]

Angiogenic Activity of Pyruvic Acid in *in vivo* and *in vitro* Angiogenic Models

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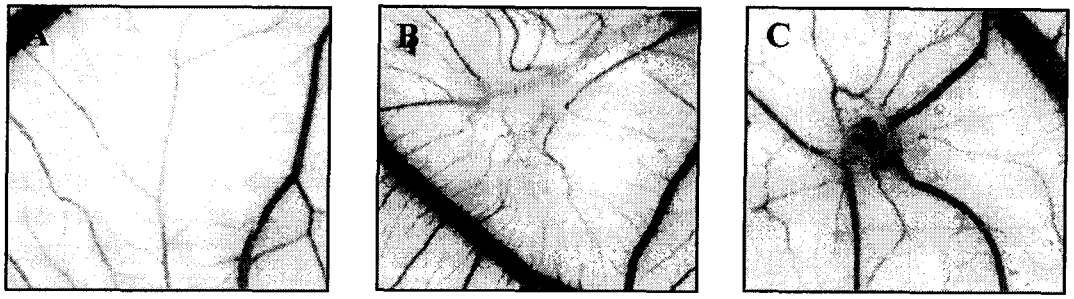
Angiogenesis, the formation of new blood vessels emerging from pre-existing endothelial vasculature, plays a crucial role in a wide range of physiological events including embryonic development, placental implantation, and wound healing for the delivery of oxygen and nutrients as well as removal of waste products. It is also initiated in response to certain pathological conditions, such as solid tumor growth, diabetic retinopathy, psoriasis and rheumatoid arthritis where angiogenesis is responsible for the progression of such diseases.

Complex and diverse cellular actions are implicated in angiogenesis, such as extracellular matrix (ECM) degradation, proliferation and migration of endothelial cells, and morphological differentiation of endothelial cells to form tubes. Although all these cascades are strictly regulated under normal conditions, abnormal high vascularization is clearly implicated in tumor growth and metastasis. The extreme growth of tumor larger than a few cubic millimeters in size requires continuous recruitment of new blood vessels. These newly synthesized blood vessels also provide a route for cancer cells to enter the blood circulation and spread to distant other organs.

In addition, one of the most important attributes of the tumor growth is its responsiveness to local metabolic changes, high rates of glucose uptake and glycolysis by upregulation of pyruvic acid transporter, MCTs, and the alterations in the glycolytic enzyme complex. The major end product of this abnormal metabolic pathway, pyruvic acid, is therefore produced in quantity and must be eliminated from the cells to permit persistent high glycolytic flux. That is, high rates of pyruvic acid production occurs in tumor and this condition may trigger neovascularization, it is of interest to determine whether pyruvic acid modulate angiogenic action of endothelial cells for growth and metastasis of tumor cells.

To test this hypothesis, we investigated an angiogenic action of pyruvic acid. We report that pyruvic acid markedly promotes angiogenesis in both *in vivo* and *in vitro* angiognenesis models. Furthermore, we show that angiogenic function of pyruvic acid is probably mediated via increasing the mRNA expression of FGFR2 and VEGF among several angiogneic activators and their receptors.



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Compounds	Dose (μg/egg)	Eggs showing angiogenesis	Total eggs tested	% of activation (mean ± SE)
Blank	-	2	43	3.3 ± 2.1
PMA	0.1	26	33	87.5 ± 12.5 *
Pyruvic Acid	1	2	15	20 ± 20
	5	4	19	24.2 ± 8.9 *
	50	5	10	50 ± 10 *
	100	13	25	51.2 ± 1.2 *
	300	30	38	80.7 ± 8.7 *

Fig. 1. Angiogenic effect of pyruvic acid on the chick CAM

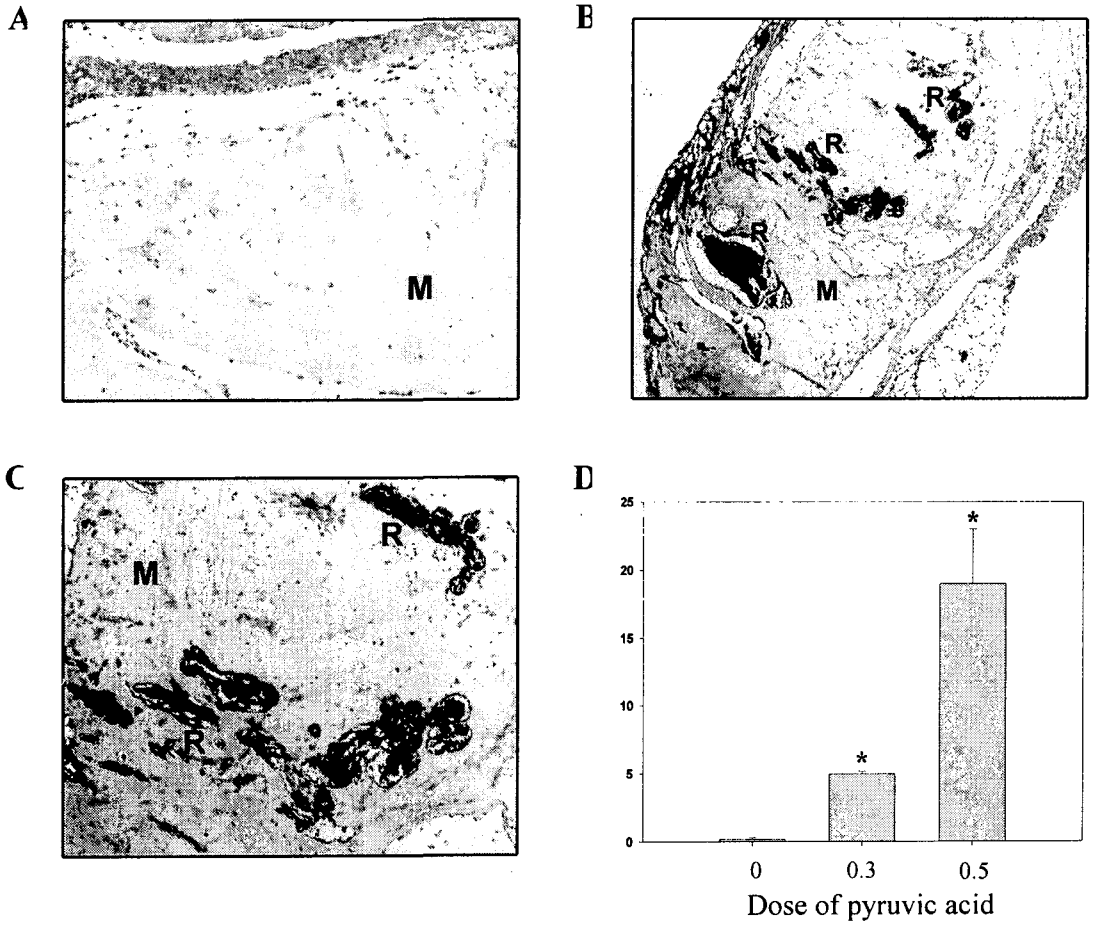

Fig. 2. Angiogenesis induced by pyruvic acid *in vivo* mouse matrigel-plug assay.

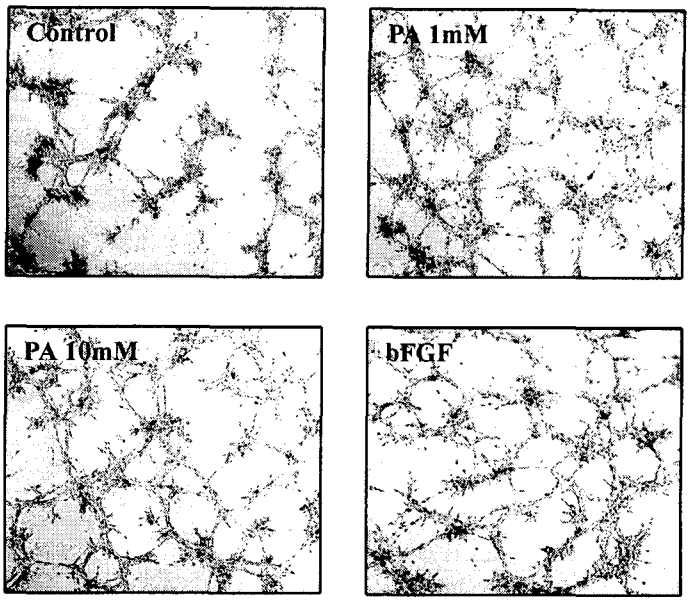

Fig. 3. Effect of pyruvic acid on *in vivo* angiogenesis of BAECs

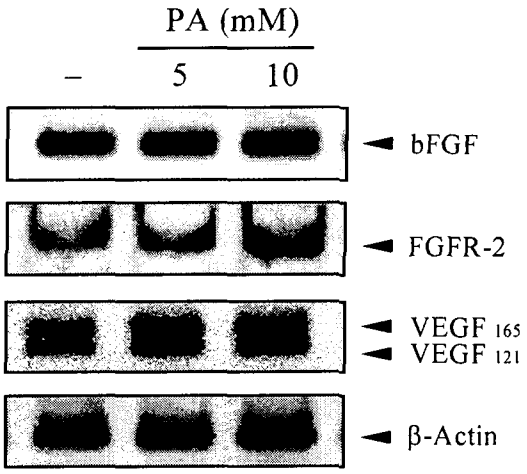

Fig. 4. Effect of pyruvic acid on the expression of angiogenesis-associated genes