ANGIOGENESIS AND METASTATIC SPREAD OF OVARIAN CANCER

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Definition and mechanism of angiogenesis

- Angiogenesis is the process of new capillaries developing from preexisting vessels.
- The mechanism of angiogenesis involves proliferation of capillary endothelial cells.

Regulation of angiogenesis

- It is a complex issue in which a delicate balance between promotors and inhibitors is maintained.
- Disturbance of this balance may result in a disrupted physiologic state or various pathologic conditions.

Source: Abulafia O,Sherer DM. Angiogenesis in the ovary. Am J Obstet Gynecol 2000; Jan V 182 N 1, 1: 240-246.

Regulation factors

Primary promotors of angiogenesis:

- vascular endothelial growth factor (VEGF)
- acidic fibroblast growth factor (aFGF)
- basic fibroblast growth factor (bFGF)

Inhibitors:

- non-specific factors: interferons, platelet factor 4
- specific: angiostatin (an internal fragment of plasminogen) and endostatin.

Source: Folkman J, Klagsbrun M. Angiogenic factors. Science 1987; 235-7.

Harris AL. Antiangiogenesis for cancer therapy. Lancet 1997; 349 (suppl. 2): SII13-SII15.

Physiology of angiogenesis

- Normal growth
- Development
- Wound-healing
- Menstruation
- Pregnancy

Source: Kohn E. Aging issues in invasion and metastasis Cancer 1993; Suppl Jan 15; V 71 N 2: 525-557.

Pathology of angiogenesis

- Benign tumor
- Tumor proliferation
- Metastasis

- Triad stimulation of capillary endothelial cells - motility, proteolysis and growth.

Source: Kohn E. Aging issues in invasion and metastasis Cancer 1993; Suppl Jan 15; V 71 N 2: 525-557.

Liotta LA, Stetler- Steveson WG. In Principles of molecular cell biology of cancer : cancer metastasis in cancer. ed. by DeVita VT, Hellman S, Rosenberg SA. Lippincott Co Philadelphia. Ch 8 : 134-149, 1993.

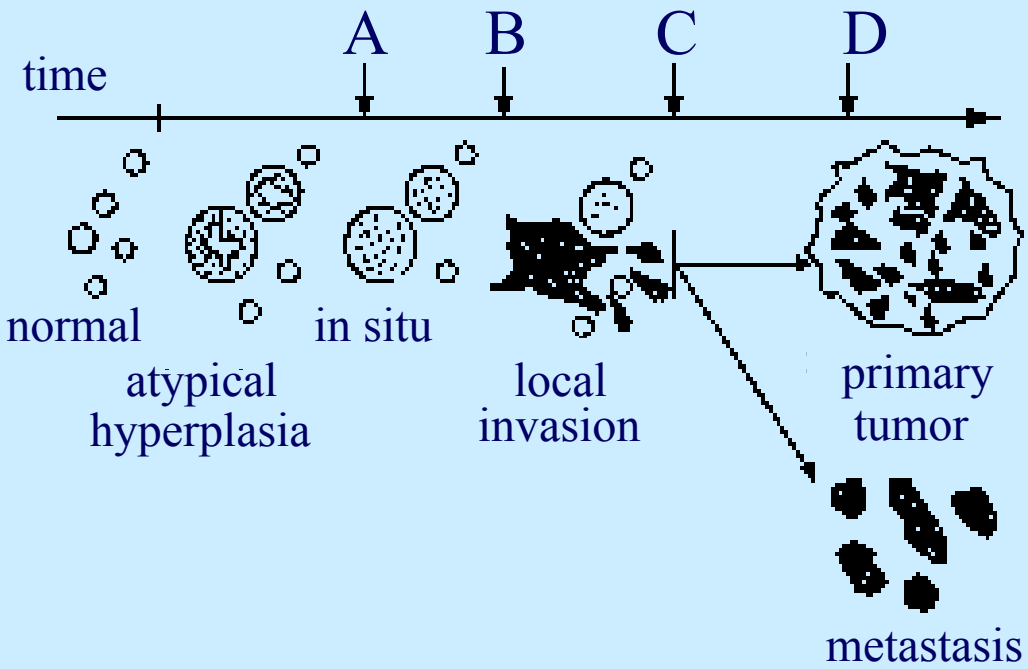
Angiogenesis in human ovaries

- Human ovaries are unique: they are the only organ in the uninjured adult body where angiogenesis occurs in a repetitive cyclic fashion.

- Angiogenesis is an essential component of both follicular and luteal phase of the ovarian cycle.

Source: Gordon JD, Schifren JL, Poulk RA, et al. Angiogenesis in female reproductive tract. Obstet Gynecol Surv 1995; 50: 688-97.

CANCER PROGRESSION

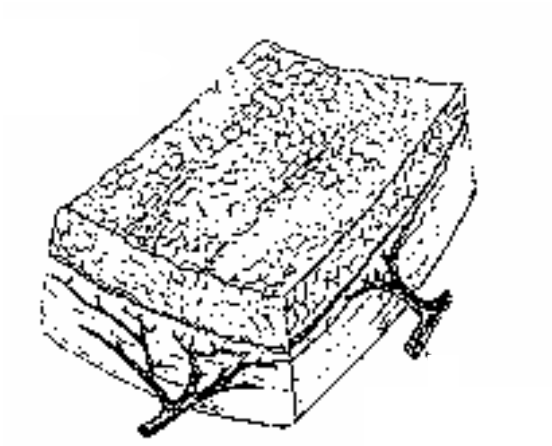


Time points:

- A=overt noninvasive carcinoma
- B= onset of local invasion
- C=onset of metastatic dissemination
- D=clinical stage II-IV

Source: Liotta LA, Tumor invasion: role of extracellular matrix. Cancer Res 1986; 46: 1-7.

AVASCULAR PHASE OF TUMORS
(years)

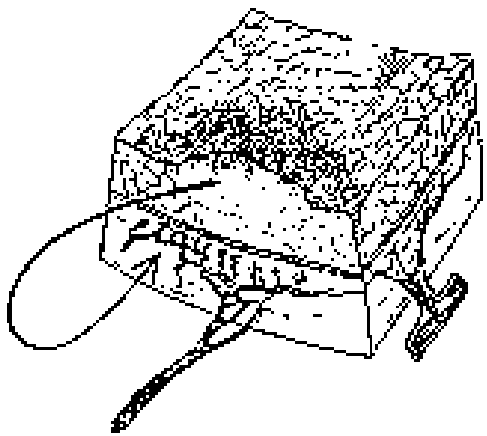


NORMAL EPITHELIAL TISSUE
AND ITS VASCULAR SYSTEM

CARCINOMA IN SITU AND VASCULAR
SYSTEM OF EPITHELIAL TISSUE

Source: Folkman J. Tumor angiogenesis: Theraputic implications. N Engl J Med 1971; 285: 1182-86.

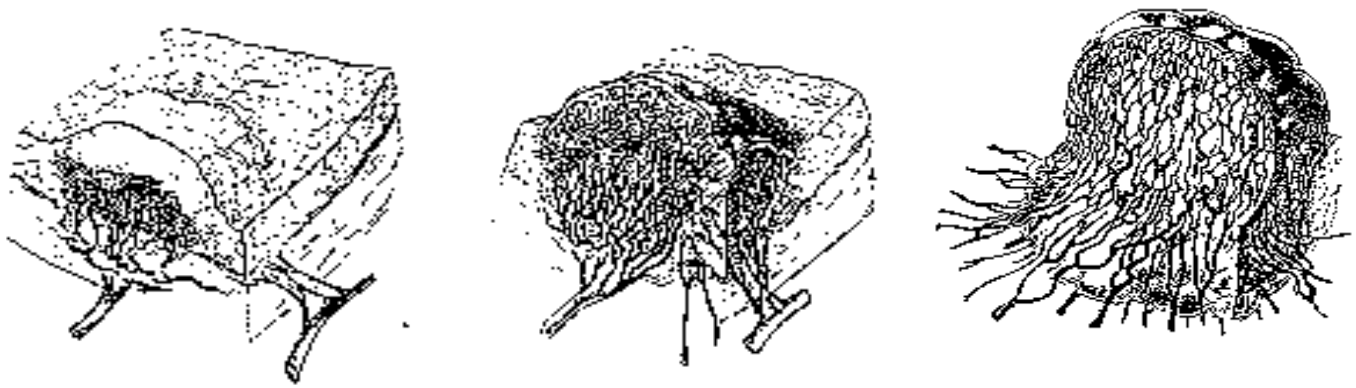
ANGIOGENESIS



TUMOR MUST RELEASE A CHEMICAL MESSENGER BEFORE NEARBY BLOOD VESSELS WILL SEND OUT CAPILLARIES THAT ARE CAPABLE OF PENETRATING TUMOR

Source: Folkman J. Tumor angiogenesis: Theraputic implications. N Engl J Med 1971; 285: 1182-86.

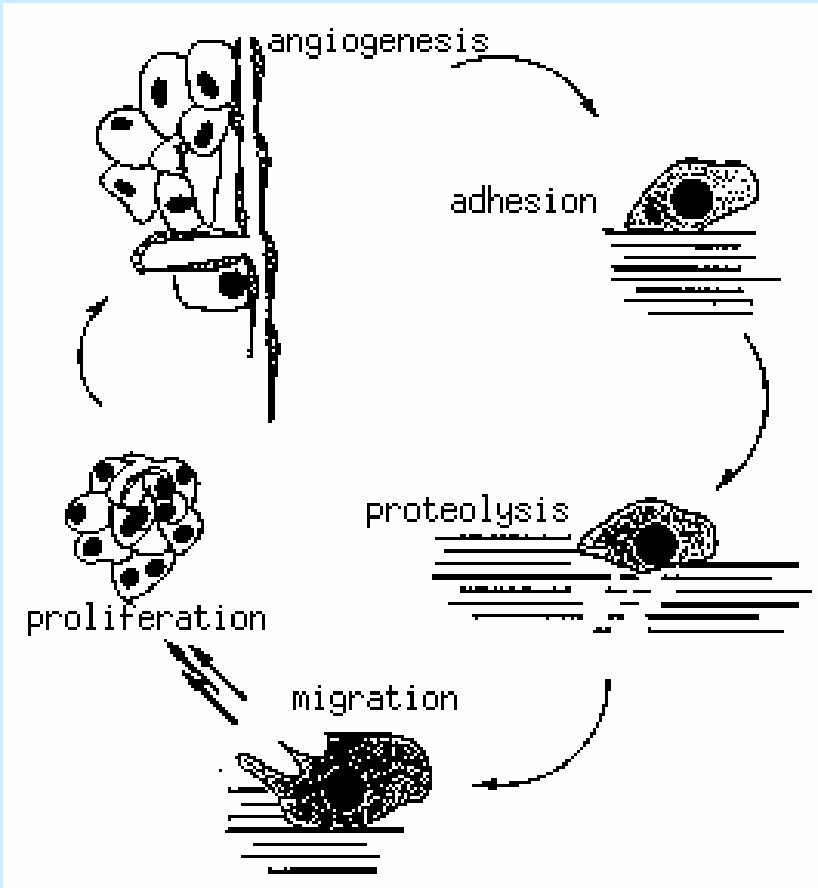
VASCULAR PHASE OF TUMOR
(months)



ONCE THE TUMOR IS VASCULARIZED RAPID GROWTH FOLLOWS

Source: Folkman J. Tumor angiogenesis: Theraputic implications. N Engl J Med 1971; 285: 1182-86.

METASTATIC CASCADE



The process of metastasis is a circular one in which the primary tumor and the metastasis can metastasize.

This cascade consist of :

- tumor - induced angiogenesis
- tumor cell adhesion to endothelial cells and vascular basement membrane (BM)
- induction of proteolytic degradation of vascular and parenchymal BM
- migration through the BM in response to tumor- and host - derived hemoattractants
- proliferation

Source: Liotta LA, Tumor invasion: role of extracellular matrix. Cancer Res 1986; 46: 1-7.

Summary:

- Physiological role of angiogenesis in ovaries is essential participation in both phases of the ovarian cycle.
- Pathological role of angiogenesis in the development of ovarian cancer is tumor growth and metastatic dissemination which consists of 5 steps of metastatic cascade.

Significance of angiogenesis

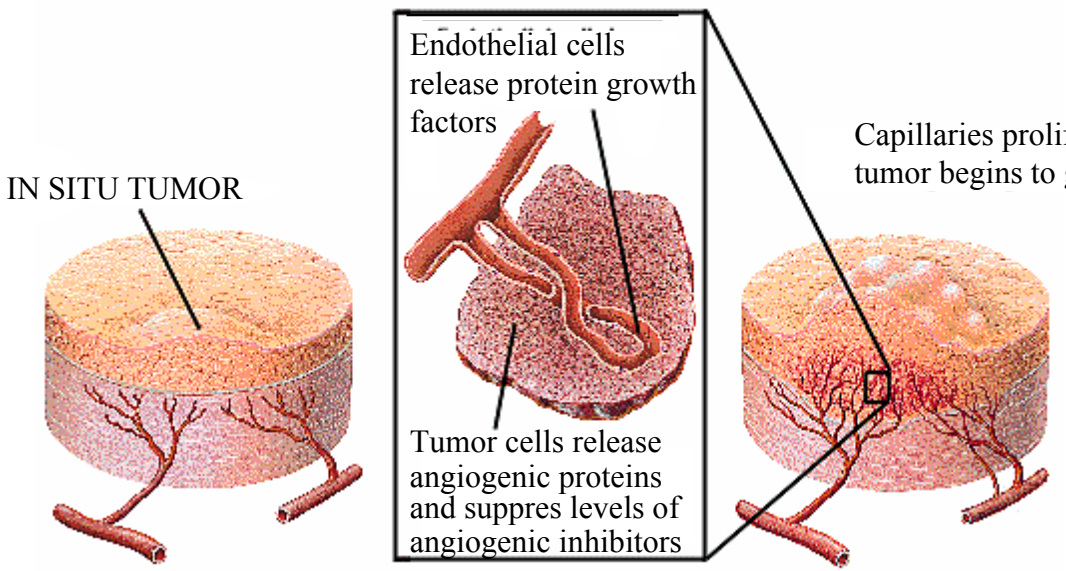
- Angiogenesis in the development of ovarian cancer has therapeutic impact.
- Therapeutic significance is a result of suppressing biological activity which can lead to restriction of the tumor.

A new approach for anticancer therapy

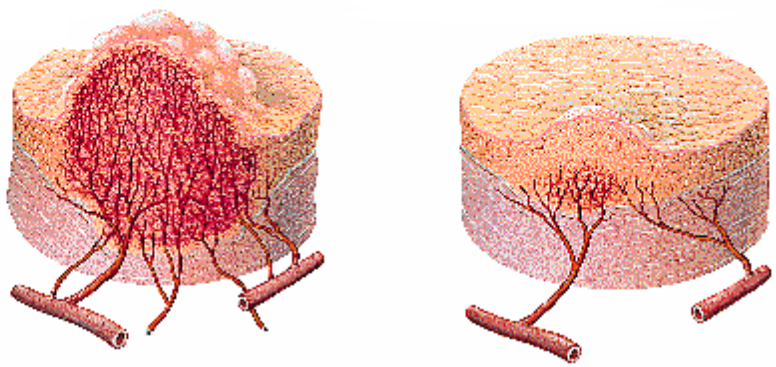
- Antiangiogenic drugs target endothelial cells while standard cytotoxic chemotherapy targets all rapid dividing cells.
- Differences in targets give advantages for antiangiogenic therapy: antiangiogenic drugs are less likely to cause symptoms characteristic of standard cytotoxic chemotherapy.
- In case of antiangiogenic therapy, drug resistance may not develop, while drug resistance is a major problem of standard cytotoxic agents.

Source: Antiangiogenesis Inhibitors in Cancer Research. Press Release of National Cancer Institute-on line. Revised April 2 1999; NCI Press Office (301) 496-6641.

THERAPIES OF THE FUTURE



Tumor continues to expand, eventually spreading to other organs



After treatment with antiangiogenic drugs, tumor diminishes in size

Adapted from: Scientific American, Sept Issue 1996; by Juda Folkman.