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Identity, Microbes & Defense
11:15 - 12:15 p.m.
Perspectives in Pathology

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HOW DO TUMORS SWITCH TO THE ANGIOGENIC STATE?

After the original hand-out was printed up...I decided to focus this lecture on a more **central** problem...that is the reason for the new hand-out labeled updated outline in right upper hand corner.

The previous hand-out is an update of last year's talk, but it mainly covers the phenomenon of angiogenesis and specifically, tumor angiogenesis as this field of research has developed. (You don't have to throw it out). :)

The reason for the change to the revised hand-out....is that certain principles about ANGIOGENESIS which have been learned from laboratory research, carried out over the past decade or so, are now beginning to help us understand in a more significant way than ever before,....how human tumors develop.

So that is what I have chosen as the theme of this lecture. And you can see in the new hand-out, . . . that I have put together **10** of these mini-principles or guidelines about the role of angiogenesis in human tumor growth, for which there is now considerable evidence in the literature.

Let me begin with a study of angiogenesis in **human breast cancer,** which Noel Weidner and I have just completed (over the past year). Dr. Weidner is a pathologist at the Brigham, very experienced in diagnosing breast cancer.

Women in the U.S. have a life-time risk of breast cancer of 1 out of 10.

Breast cancer is **epithelial** in origin and is **multifocal** in presentation. Therefore, it has some similarities to other carcinomas, such as bladder, colon, prostate etc, (all of them also epithelial and multifocal).

We studied specimens of INVASIVE breast cancer from patients presenting 10 years ago (so we could know the current outcome),...we re-cut the paraffin blocks of tissue, but re-stained them with antibody to FACTOR VIII antigen, (a specific marker for vascular endothelial cells).

This had not been done before, and revealed some very interesting information.

Slide 1: Here is a conventional H&E of human breast, and here, vessels stained.

Slide 2: In summary, the human breast has about 10,000 ducts, with 2 cell layers, (of which only the basal cell layer proliferates).

(i) You can have **carcinoma in-situ** without angiogenesis or with angiogenesis;

(ii) You can see **invasion** without angiogenesis, or with angiogenesis.

The **1st** point we learned is that the SWITCH to the angiogenic state occurs in different ducts at different times, I.E., there is heterogeneity for angiogenic activity! (And also we have ~~compelling~~ experimental evidence). ~~for~~ This also (show you data)

The **2nd** point is that the ONSET of angiogenic activity seems to behave as an independent event. (It is a visible example of the sequential ~~events~~ steps that Vogelstein has described.

→In the breast it can come ON before or after invasion.

→In other tumors it can appear even before malignant transformation (e.g., adrenal adenoma), or coincident with malignancy (e.g., melanoma), or after malignant transformation (e.g,. carcinoma *in situ*.) breast, bladder, cervix

The **3rd** point is that where invasion had begun, it was the onset of angiogenesis that permitted EXPANSION of the tumor cell population, and not the other way round. Where there was no angiogenesis, there was no tumor mass larger than a few millimeters.

And, finally a **4th** point that we learned, was that in those specimens where angiogenic activity was low, or had not switched on above background, METASTASIS was low or non-existent. BUT, the switch to the angiogenic state PERMITTED distant metastases (brain, lung, bone)...and increasing angiogenesis, correlated with increasing metastasis.

Slide 3: And here one can see, that virtually 100% of patients with highly angiogenic lesions subsequently developed metatases, . . . whereas those with little angiogenic activity had few or no metastases.

Slide 4: Carcinoma in situ before neovascularization.

Slide 5: Carcinoma in situ after neovascularization.

Slide 6: Huge mass of invasive carcinoma with angiogenesis.

Slide 7: In a breast specimen which already had a large carcinoma HERE, is the VERY BEGINNING OF CARCINOMA & IT IS UNDERGOING A SWITCH TO THE ANGIOGENIC STATE!

"DO we have experimental evidence that tumor GROWTH is angiogenesis-dependent, i.e., that angiogenesis permits EXPANSION of the tumor cell mass?".....YES>>>>>>>

Slide 8: An elegant experiment in the early 1970's by Michael Gimbrone when he was a student in our lab..implanted V2 carcinoma in the anterior chamber of rabbit eye. Remained viable, unable to expand beyond 0.5 mm, ...UNLESS it was moved to the vascular bed of the iris, and then it grew to 16,000 times its original tumor volume in 2 weeks! (Analogy = retinoblastoma)