Introduction to Cancer & Cancer Research

Lecture 12

Cancer

Tumor types:

Benign: “grew locally without invading adjacent tissues”

Malignant: “invaded nearby tissues and spawned metastases”

Primary tumor: “site where the disease of cancer began”

Types

Carcinoma: found in body tissue known as epithelial tissue that covers or lines surfaces of organs, glands, or body structures (>80%)

Sarcoma: a malignant tumor growing from connective tissues, such as cartilage, fat, muscle, tendons, and bones

Lymphoma: originates in the nodes or glands of the lymphatic system, whose job it is to produce white blood cells and clean body fluids, or in organs such as the brain and breast

Leukemia: of the bone marrow that keeps the marrow from producing normal red and white blood cells and platelets

Myeloma: in the plasma cells of bone marrow. In some cases, the myeloma cells collect in one bone and form a single tumor

Causes

"the interaction of many factors" – "the factors involved may be genetic, environmental, or constitutional characteristics of the individual"

Occupational: 2%

Lifestyle:

- Tobacco: 34%
- Diet (low veg., high nitrates, salt) 5%
- Diet (high fat, low fiber, fried foods) 37%
- Tobacco and alcohol 2%

Carcinogen(1940): cancer causing; chemicals, viruses, radiation, power lines (magnetic fields)?, radio waves – electromagnetic radiation (cell phones)?

Growth

1950's – primary growth around blood vessels (0.2 mm)

Cancer cells synthesize: vascular endothelial growth factor (VEGF)

Tumors "design the layout of their own vasculature, doing so step-by-step as the grow"

Angiogenesis: and thus anti-angiogenic factors

Medical Research Subjects (sources)

Men, Women, Minority Groups

Children

Prisoners

students

The Poor

Terminally Ill

Animals

Tissues from all of the above

Cells

Clinical Trials and Basic Research

- ≈ $182B /year on medical research in US
- Effectiveness and side effects are measured in human subjects
  - Drug (most common), surgery, device, special diet…
- Regulations (Food & Drug Administration – FDA)
- Pre-clinical and clinical testing
  - Animals – toxicity, effects on organs, whole animal
  - Promising? – "Therapeutic Index" → clinical trials
  - National Cancer Institure (NCI) portion of NIH has over $6.56 billion budget/year alone out of $42B.

Clinical Trials

- Phase I – 10-80 people – determine side effects and dose – "safe"
- Phase II – 100-300 – "safe *and* effective"
- Phase III – 1000-3000 – Effectiveness, monitor side effects, compare to accepted therapies
- Goal: Exclude "Bias", "placebo effect", "double-blind" → Ex: "blind taste test" for Pepsi vs. Coke
  - Blind or double-blind?

Cancer Research (on animals)

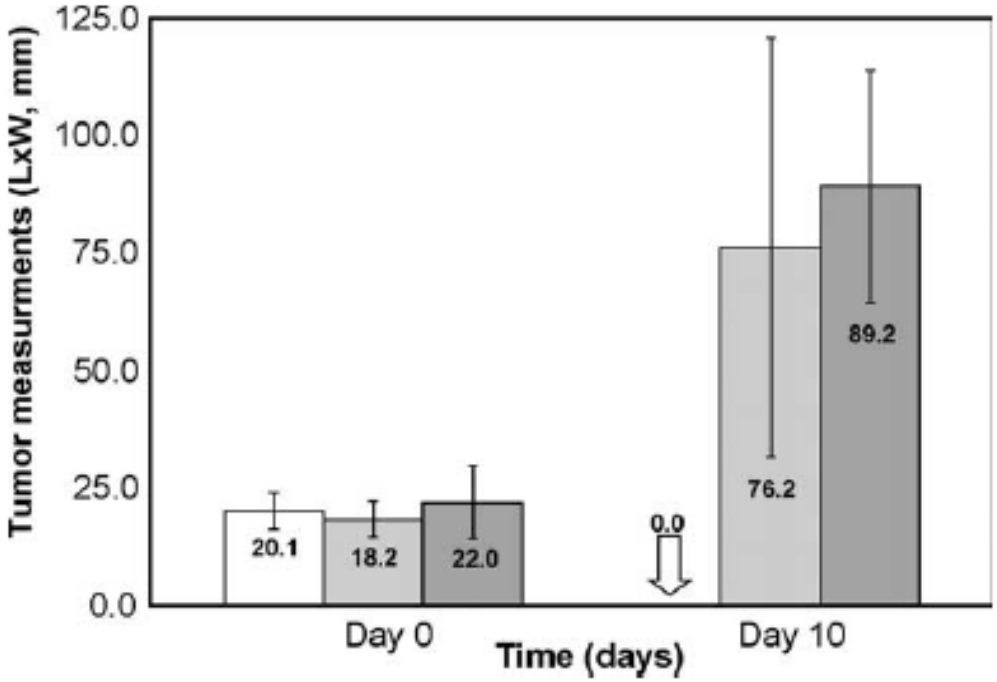


Fig. 1. Mean tumor size measured on treatment day and 10 days later for 25 tumors. All tumors which were treated using NAPT showed complete necrosis by day 10. One standard deviation is shown. NAPT treatment group ($n = 7$), sham treatment group ($n = 8$), untreated controls ($n = 9$).

Randomized Clinical Trial

Can you serve as Physician and scientist at the same time?

Ex: End-stage cancer, for which there is no treatment; the control group either gets a placebo or a poor treatment.

What the physician “feels, suspects, believes, has a hunch about” is not relevant.

Idea of Cancer as an Inflammatory Disease

Positive/Negative Feedback Factors in Inflammation and Cancer:

-Precancerous inflammation can cause increased genetic and ***epigenetic*** damage. (be able to define epigenetic)

-Aberrant oncogenic signaling can induce inflammation

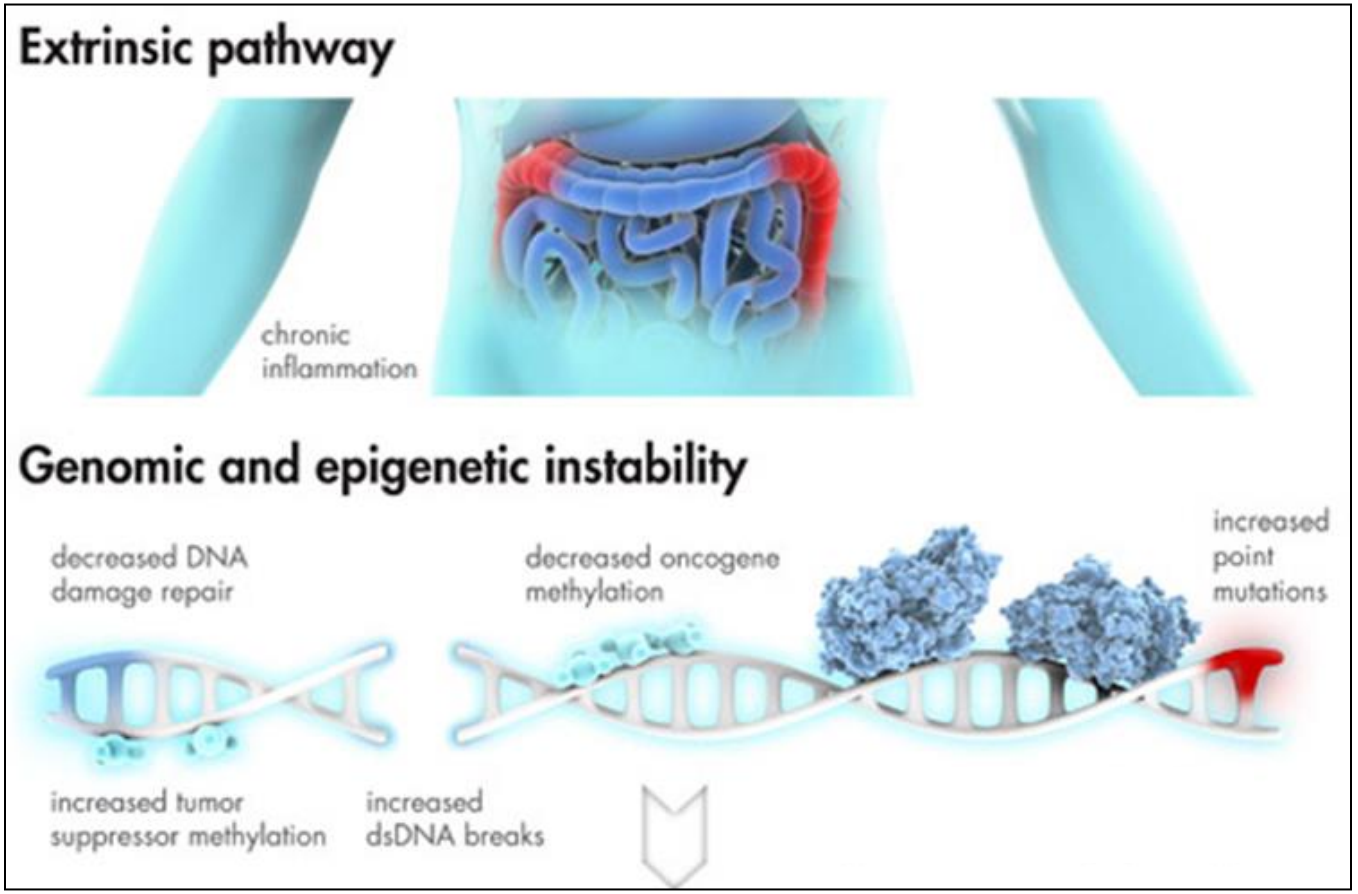
-The inflammatory response in cancer tissues elicits tumor tissue remodeling and metastases (almost like a wound/healing gone bad).

Idea of Cancer as an Inflammatory Disease

Cancer related inflammation can fall into one of two categories: 1. precancerous inflammation lesions and 2. inflammation that is present in almost all cancer tissues including those that have no precancerous inflammation lesions.

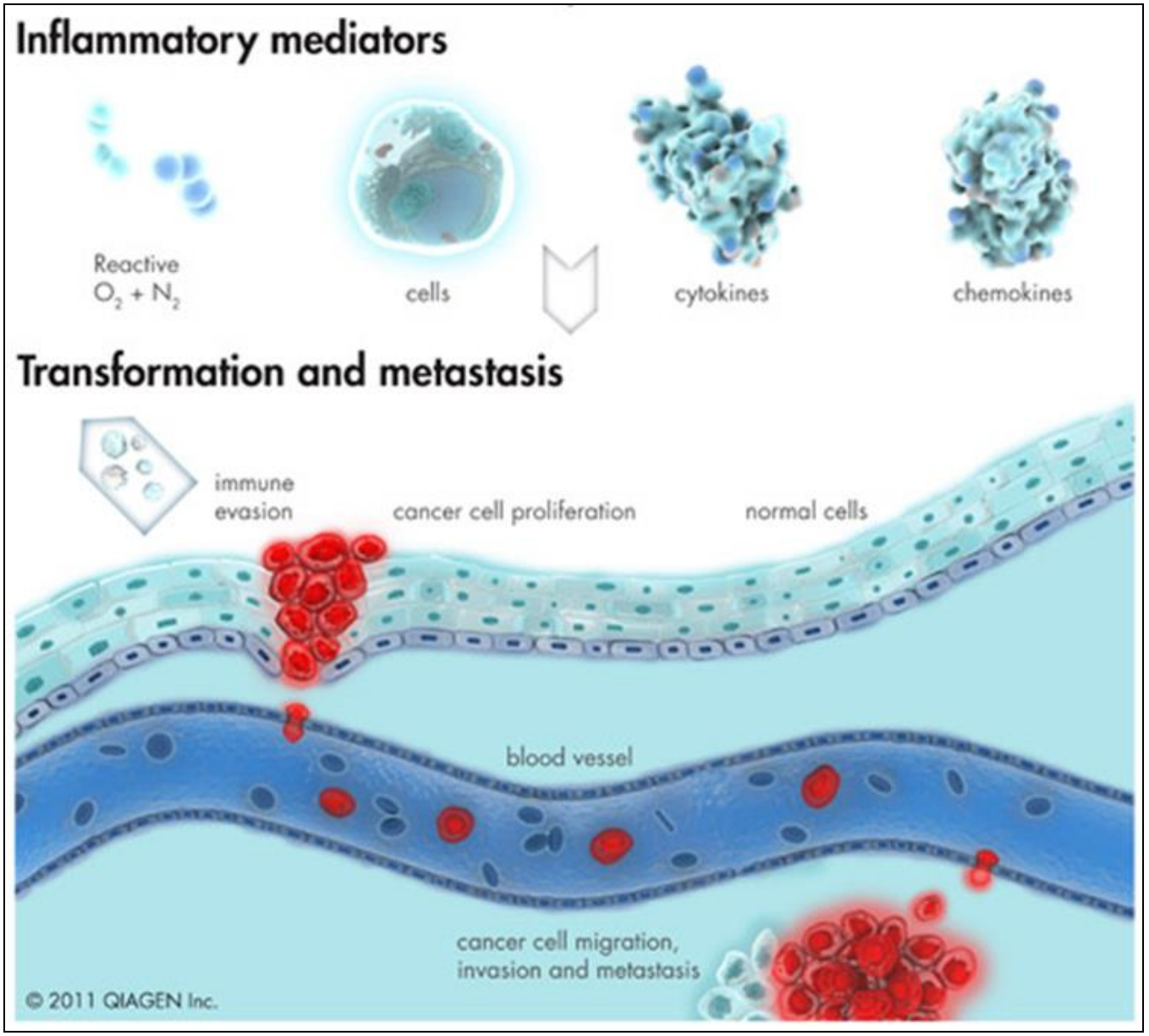
The connection between inflammation and cancer can be thought of as consisting of two pathways: an extrinsic mechanism, where a constant inflammatory state contributes to increase cancer risk (such as inflammatory bowel disease), and an intrinsic mechanism, where acquired genetic alterations (such as activation of oncogenes) trigger tumor development.

Idea of Cancer as an Inflammatory Disease-2



What does ***methylation*** do?

Idea of Cancer as an Inflammatory Disease-2

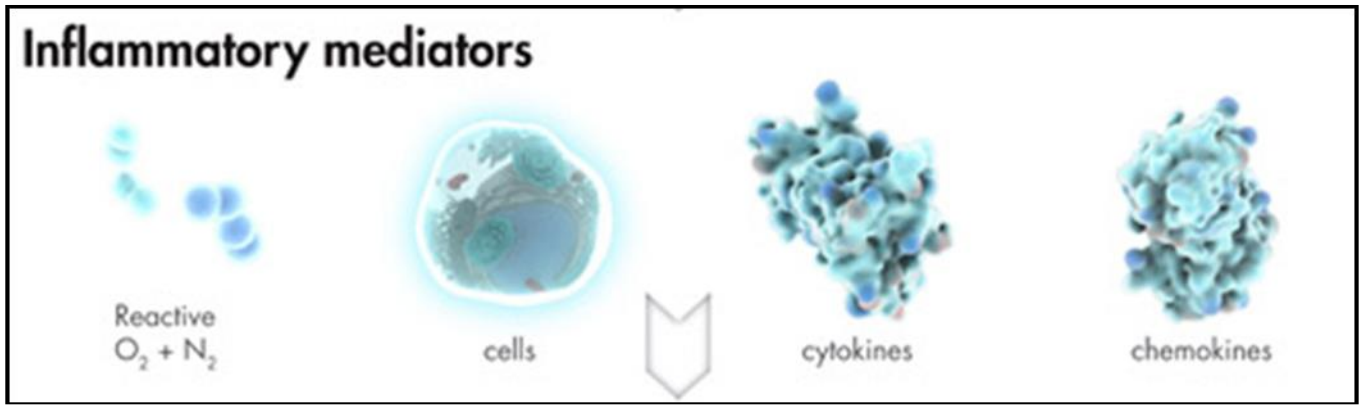


Idea of Cancer as an Inflammatory Disease-2

- The former (extrinsic) inflammatory pathway can ***increase the risk*** to cancer development

- The latter (intrinsic) inflammatory pathway is ***necessary to maintain and promote*** cancer progression.
- The idea (theory) is that both precancerous inflammation and inflammation stemming from genetic alteration can cause cell transformation and promote tumor progression.

Idea of Cancer as an Inflammatory Disease-2



- ***How*** would oxidizing compounds affect cancer?
- Increased cancer risk is attributed to the observation that chronic inflammation can cause genetic damage via production of oxidizing compounds, such as reactive oxygen and nitrogen species. These products can induce the formation and accumulation of mutagenic, toxic, and/or genome-destabilizing DNA lesions.
- Inflammation related signalling has also been shown to ***suppress*** the activity of the DNA damage repair system.

Aberrant oncogenic signalling can induce inflammation

- To obtain a malignant phenotype, the cell needs to 1): acquire genetic or epigenetic mutations to trigger transformation. Then 2): this malignant phenotype must be maintained.
- The inflammatory response in cancer tissues plays an important role in ***maintaining the phenotype*** by inducing tumor tissue remodeling, angiogenesis, and metastasis; all the while suppressing the innate anticancer immune response.

Inflammation and Cancer- example pathway

- The NFκB signaling pathway is a key coordinator of innate immunity and inflammation. NFκB signaling plays crucial roles in both precancerous chronic inflammation as well as cancer induced inflammation.

- Frequently *activated by cancer gene mutation,* NFκB is an important regulator of tumor initiation and progression.

- Activation of this pathway induces expression of inflammatory cytokines, adhesion molecules, enzymes in the prostaglandin-synthesis pathway (such as COX2- what blocks this?), inducible nitric oxide synthase (iNOS), angiogenic factors and anti-apoptotic genes (such as Bcl-2).
- _Be able to list or identify these components as positive or negative feedback modulators in the progression (or regression) of cancer.

End!