

Connections Between Autoimmune Disease & Cancer

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Dr. Reetesh Bose, PGY2

Supervisor: **Dr. Jennifer
Beecker, MD, CCFP(EM),
FRCPC, DABD, FAAD**

University of Ottawa,
Division of Dermatology

Outline

Definitions and Concepts

Cancer

- Types and statistics
- Diagnosis and treatment
- Cancer immunotherapy
- Paraneoplastic syndromes

Autoimmunity

- Types and statistics
- Diagnosis and Treatment
- Cancer and Autoimmune disease: The good, the bad, and the ugly
- Auto-immune disease, inflammation, and cancer

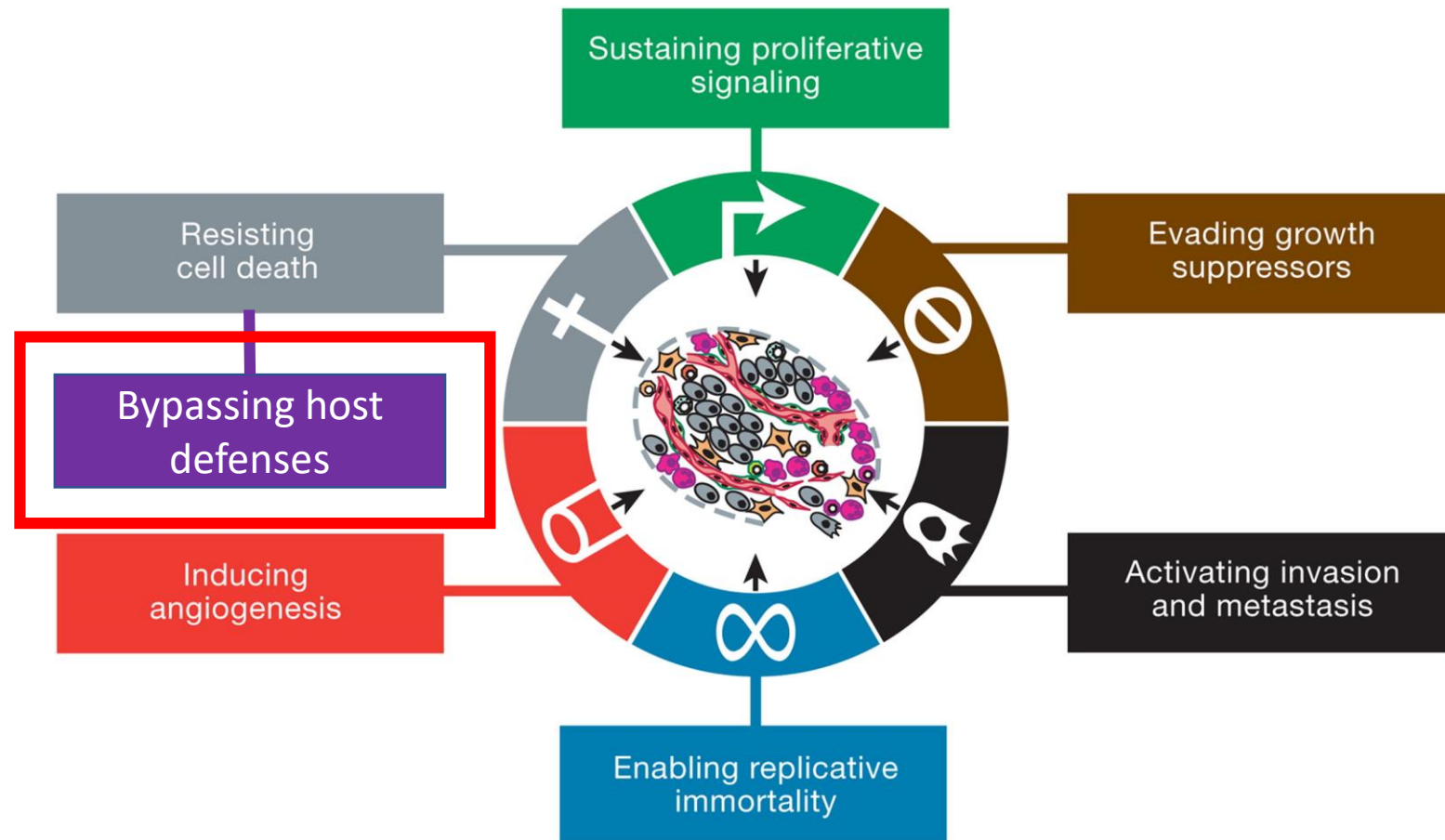
Conclusion and Questions

Definitions and Concepts: Cancer

Cancer: a collection of related diseases where an altered colony of cells arise from normal body cells, dividing without stopping and spreading into surrounding tissues competing for space, and nutrients.

6 Hallmarks:

1. Sustained proliferation
2. Evading growth suppressors
3. Invasion + metastasis
4. Replicative immortality
5. Angiogenesis
6. Resisting cell death
 - Bypassing host defenses



*Strong association with cellular stress, inflammation, carcinogens and our inherited capacity to deal with these stressors

Definitions and Concepts: Immunology

Immune system: A network of cell (white blood cells, AKA WBC) working together to protect the body from threats such as infections (bacteria, viruses, and the basis of how vaccines work)

- **Innate:** Immune cell types with a rapid response to all stimuli deemed foreign
- **Adaptive:** Immune cell types with a learned response to specific, previously encountered threats via **antibodies**.

Antibodies: Proteins produced by immune cells to allow them to identify and target threats.

Inflammation: The immune system's response to a perceived threat. Can be protective, but chronic, uncontrolled activation can have damaging effects.

Autoimmune Disease: When the immune system mistakenly attacks normal body cells. This causes inflammation and tissue damage.

Cancer and Autoimmune disease
are both common, highly
inflammatory conditions.

Cancer: Types and Statistics

Type	New cases per 100,000	Mortality per 100,000
1. BREAST	67	11.8
2. LUNG	55.8	44.7
3. PROSTATE	54.7	8.1
4. COLORECTAL	40.1	14.8
5. MELANOMA	22.3	2.7
7. Non-Hodgkin's lymphoma	19.5	5.9

Cancer: Diagnosis and Treatment

Diagnosis:

- Symptoms (examples): Location specific, often silent until later stages of disease
 - Persistent cough (blood), altered bowel habits, bone pain, growths, non-healing sores, fever, weight loss, night sweats.
 - Clinical Assessment: History, physical exam, blood tests
- Imaging: U/S, X-ray, CT scan, MRI, nuclear uptake scans.
- Biopsy: Diagnosis and tumor grade (also tumor stage, TNM after surgery)

Treatment:

- Patient-centred approach
- Conservative: Supportive, symptoms relief, psychologic, social, alternative
- Medical: Chemotherapy, radiotherapy, immunotherapy, Chemo-immunotherapy fusion drugs
- Surgical: Excision/resection, lymph node removal

Cancer: Immunotherapy

- Introducing antibodies* that:
 - Inhibit the “hallmarks”, cancer cells use for survival
 - Activating an immune response against cancer cells

* Antibodies that bind unique cancer cell proteins or proteins expressed in very high levels in cancer cells compared to host tissue.

- Sustained, excessive immune cell activation carries the risk of producing immune cells directed against our body
- This results in auto-immunity, in some cancers this closely resembles auto-immune diseases

Autoimmune disease

Definition: When the immune system mistakenly attacks our body, causing damage.

Unknown cause, but numerous theories have been developed:

- 1) Genetic and environmental factors: Both important
- 2) Uncontrolled, inappropriate immune cell activation
- 3) New WBCs mistakenly directed against host tissue are formed
 - Usually the WBC would be destroyed in a process known as tolerance
- 4) Some cancers cause autoimmunity via abnormal signalling (paraneoplastic)
 - Cancer therapy can also increase the risk of cancer. Cytotoxic chemo, and radiation therapy all cause DNA damage, leading to cancer, but also can induce autoimmune disease.
 - In autoimmunity, perpetual untreated activation may cause tissue damage leading to chronic inflammation, and subsequently increase the risk of cancer

Autoimmunity: Types and Statistics

More common:

Psoriasis/psoriatic arthritis

Lupus

IBD

Rheumatoid arthritis

Multiple sclerosis

Less common:

Dermatomyositis

Sarcoidosis

ALS

Epidermolysis bullosa

Paraneoplastic Syndromes: (Autoimmunity due to cancer)

Lambert-Eaton Syndrome

Necrolytic migratory erythema

Paraneoplastic pemphigoid

Autoimmune disease:
Diagnosis and Treatment

Diagnosis:

Symptoms: Any tissue can be affected, broad range of severity. Extremely complex cell signalling issues.

Assessment: History, physical exam, blood tests, inflammatory/autoimmune markers

Imaging: ultrasound, X-ray, CT scan, MRI, nuclear uptake scans.

Biopsy if needed to see what cells are involved and the level of tissue damage occurring.

Treatment:

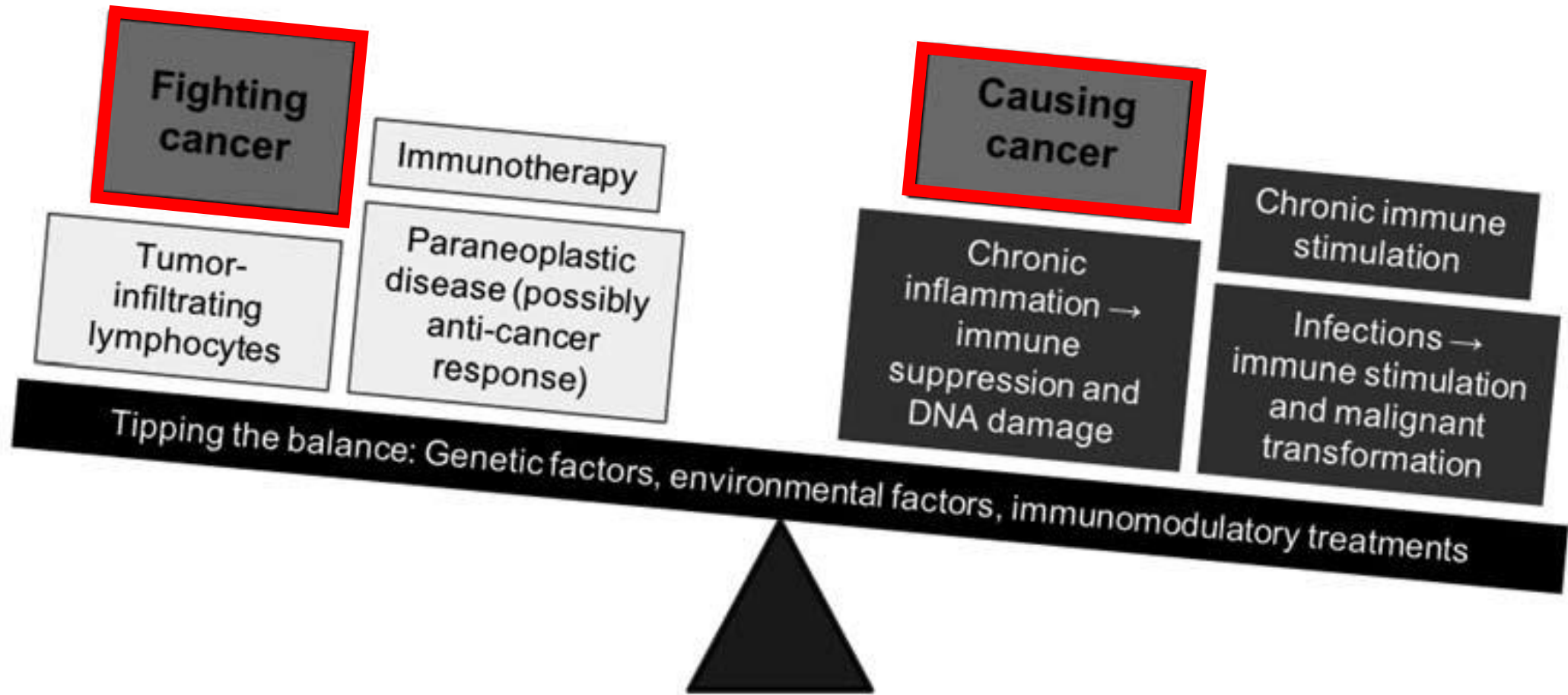
bio-psycho-social,
patient-centred
approach

Conservative: Supportive, symptoms relief, psychologic, social, alternative

Medical: Anti-inflammatory, immunosuppression, immunotherapy, light and laser.

Surgical: Replace/remove, organ transplant,

Autoimmunity: Cancer and Autoimmune disease



Autoimmunity: Cancer and Autoimmune disease

- Cancer and autoimmune relationship has been known for years
- Some immune function is anti-cancer
 - Specific WBCs (T-cells) in the tumor environment interact with antibodies on the tumour, which signals the WBCs to attack the tumor.
 - Numerous observations suggest that the immune system has a role in inhibiting cancer progression:
 - E.g. Patients on long-term immunosuppressive medications have an increased risk of cancer (e.g. cyclosporine for preventing graft-versus-host disease after organ transplantation, immunocompromised by HIV, cancer developing in transplanted organs)
- Auto-immunity is generally anti-cancer, but pro-cancer at the site of auto-immune tissue damage
 - A state of perpetual activation, immune mediators, such as cytokines, chemokines and free radicals, may cause tissue damage leading to chronic inflammation, and subsequently increase the risk of carcinogenesis.
 - Other factors affecting immune activity, such as genetic mutations, environmental exposure, and immunomodulatory treatments
- All result in focal (organ specific inflammation) and systemic cancers: celiac GI cancer, Lupus kidney cancer, MS brain cancer
 - SLE, MS and RA seem to reduce risk of overall cancers, but focally have higher rates due to organ specific inflammation

Autoimmunity: Cancer and Autoimmune disease...The good

- Tumor infiltrating lymphocytes (TIL) in most tumors directly correlates with improved prognosis and patient survival.
- This phenomenon, under control, **reduces overall cancer risk** by using the bodies immune system to destroy cancer cells.
- Organ specific damage and inflammation resulting from auto-immune disease does have increased cancer risk.
 - E.g. Overall cancer risk is lower in rheumatoid arthritis, but rates of lung cancer are higher (lungs are subject to autoimmune cell damage in Rheumatoid)
- Immunotherapies that increase immune activation (TILs) is an effective form cancer treatment with less side effects
- Regulatory T-cells are immune cells tell T-cells what is self-and what is foreign (Tolerance)

Autoimmunity: Cancer and Autoimmune disease... the bad

- Tumor escape: The immune response no longer targets the neoplasm.
- Regulatory T-cells (Tregs): Suppress immune activity and migrate into tumors and draining lymph nodes, dampening the antitumor immune response.
- Depletion of Tregs from tumors results in a decrease in immunological tumor-tolerance and improved antitumor immunity.
- Alternatively, successful antitumor responses may cross-react with normal self tissues, losing self-tolerance.
 - If the magnitude of the immune response continues to enlarge, inflammatory or autoimmune disease may develop

Autoimmunity: Cancer and Autoimmune disease... the ugly

- Extreme immune activation induces inflammation and autoimmunity, often correlating with the effectiveness of cancer treatment.
- Chronic inflammation is a feature of cancer, autoimmunity and other chronic illnesses (diabetes, atopy, atherosclerosis, allergies), which increase cancer risk as well as exacerbate autoimmune states
- Autoimmune disease is a cancer risk, but treatments also sometimes carry a cancer risk.
 - Therefore very difficult to separate the two to calculate true cancer risk for either.

*The fight for moderation amongst complex signalling pathways is a major challenge

Auto- immunity, Inflammation, and Cancer

Many other autoimmune or inflammatory conditions are associated with increased risk for cancers of the organs targeted by the inflammatory condition

Celiac disease targets the gut and is associated with an elevated risk of gastrointestinal malignancies, but this reduces with a gluten free diet

In Lupus, overall cancer risk is not significantly higher, but kidney and brain cancers are higher in these patients.

RA frequently experience chronic lung tissue inflammation, eventually leading to interstitial lung disease, resulting in increased lung cancer risk

Autoimmune and Cancer: Research endeavours

Treating/manipulating self-tolerance: Addressing the basis of Autoimmunity.

Develop treatments for cancer and autoimmune disease with a higher degree of specificity, reducing the unwanted effects related to adjoining cellular pathways and auto-immunity

Use engineered methods to target cancer: Monoclonal antibodies, small molecules, oncolytic viruses, drug-antibody conjugates, identifying unique biomarkers to target for therapies.

Conclusions:

1. Cancer and autoimmune disease are common and extremely important entities
2. They are not completely separate and a connection is well documented
3. The connection involves very complex signalling networks between the immune system, pathogens (bacteria, viruses, etc), and normal cells.
4. Chronic inflammation is common to autoimmune disease and cancer.
5. A lot more is left to do and even more to understand, but **the future looks bright.**

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Questions?