Age Group: 13-15

Carolina Cancer Champions Inflammation and Cancer

Nalini Dutt[1], Hermella Demsie[1], Dheepthi Mohanraj[1], Bhushan Mohanraj[2]

Ardrey Kell High School[1], Randolph Middle School[2]

Corresponding author:
Dr. Lopamudra Das Roy
Questions, please reach out:
lopa@breastcancerhub.org

Abstract:

Background: Chronic inflammation and chronic diseases contribute to the onset and progression of cancerous growth of the cells and increase the risk of cancer death. **Aim:** Analyze the correlation between chronic inflammation and the development of cancer. **Methods:** A systematic search of PubMed, AACR Journal, CancerNetwork and WHO sites. **Discussions:** Multiple articles were analyzed to understand the cancer proliferation by chronic inflammatory diseases such as Arthritis, and its effect in primary and metastasis of breast cancer. Also, inflammatory biomarkers and blood serum cytokines: TNF alpha, IL-1ra, IL-6, IL-8, IL-10 as well as CRP data were investigated. **Conclusion:** It is clear that many studies have proven that cancerous growth are triggered and spread by underlying chronic inflammatory disorder and chronic disease. These findings suggest that the increased levels of inflammatory markers are more strongly associated with the risk of cancer. By understanding the tumor cells behavior which is similar to natural inflammation responses new anti-inflammatory therapeutic approaches will be helpful in curtailing the growth of cancerous cells or to prevent altogether.

Overview of Inflammation:

Inflammation is a healthy process, essential to the body's ability to heal itself. As a natural response, the immune system releases white blood cells and chemicals to fight off the infection or repair damaged tissue. Inflammation becomes chronic by infections that don't go away, abnormal immune reactions to normal tissues, or certain conditions like obesity.

Cancer-causing chronic inflammation stems from a disease characterized by inflammation like colitis, pancreatitis and hepatitis. In these diseases, immune cells create highly reactive molecules containing oxygen and nitrogen that can damage DNA. Inflammation also may cause cells to divide.

Chronic inflammation also may result from a chronic infection, like H. pylori, which is linked to stomach cancer, and hepatitis B and hepatitis C which are linked to liver cancer. HIV increases the risk of other viruses and very rare cancers, including Kaposi sarcoma, non-Hodgkin lymphoma and invasive cervical cancer.[3]

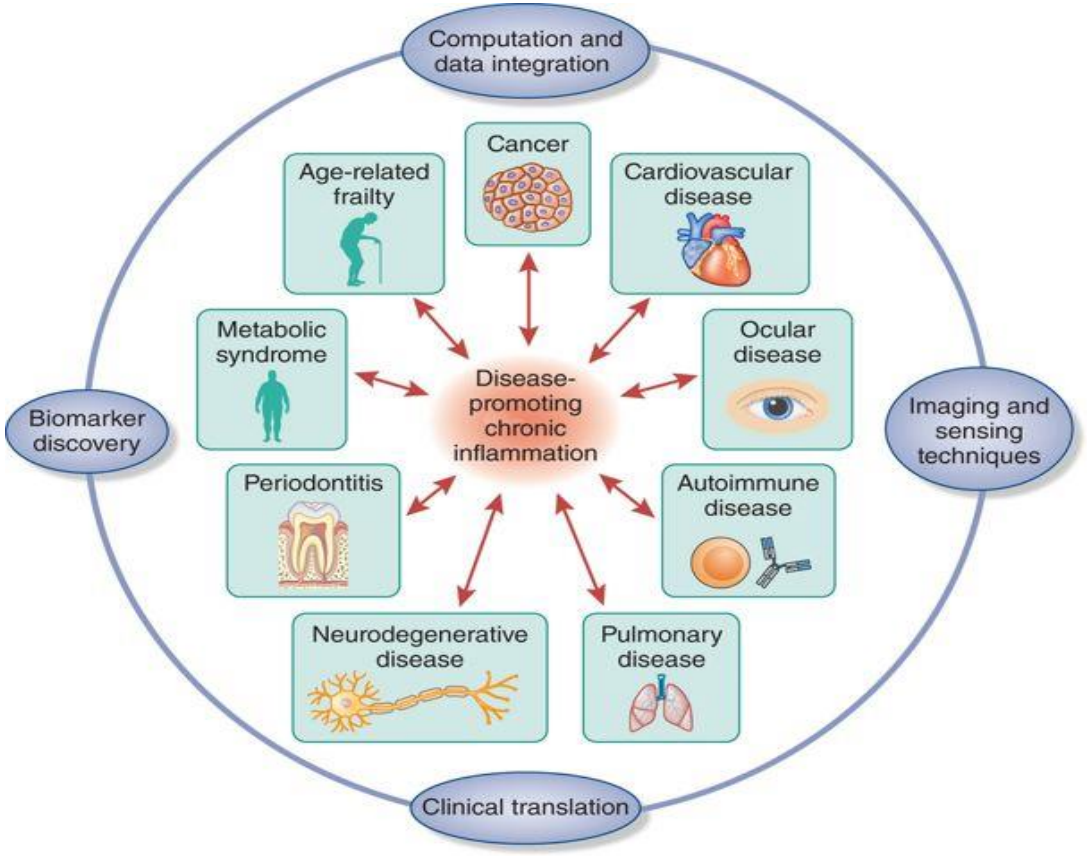
Neoplasm - Progression to Cancer

- A neoplasm/tumor is an abnormal new growth of cells. The cells in a neoplasm usually grow more rapidly than normal cells. As they grow, neoplasms can impinge upon and damage adjacent structures. It can be benign (curable) or malignant (cancerous).
- Chronic inflammation drives tumor cell initiation through direct mutational and indirect molecular effects.
- Dysregulated host inflammatory reactions induce the elaboration of reactive oxygen/nitrogen species and cytokines, which contribute to carcinogenesis through mutational and epigenetic effects.

Neoplasm - Progression to Cancer

- Primary tumor growth and neoangiogenesis is supported by tumor microenvironment (TME) infiltrating immune cells, including tumor-associated macrophages, myeloid-derived suppressor cells, neutrophils and regulatory T cells.
- **Chronically activated proinflammatory cells in the TME contribute to the metastatic potential of cancer.**
- In order to decrease cancer incidence, known risk factors that induce chronic inflammation should be avoided (i.e., exposure to environmental hazards, infectious organisms and diet).

Neoplasm - Progression to Cancer

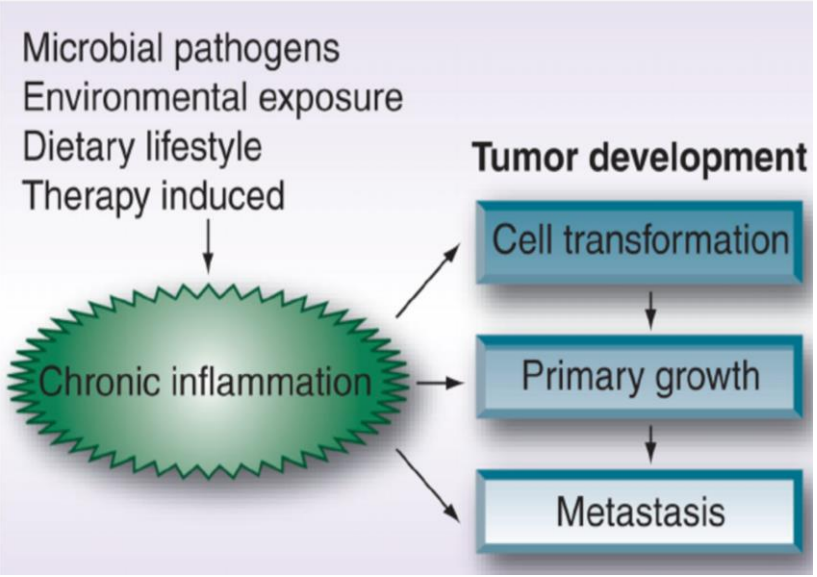


Potential contributors and therapeutic targets:

- Accumulation of senescent cells
- Unresolved infection
- Dysbiosis
- Activated microglia and macrophages
- Cytokine and chemokine dysregulation
- Imbalance between pro-inflammation mediators and pro-resolution mediators
- Gene mutations
- Epigenetic modifications
- Lifestyle risk factors

[8]

Role of chronic inflammation in cancer development



Chronic inflammation initiates, and impacts all major stages of tumor progression, from cell transformation to widespread metastasis. The cause of chronic inflammation varies by individual and includes exposure to infectious microorganisms and harmful chemicals.

[1]

Chronic inflammatory conditions associated with neoplasms

- Chronic ulcerative colitis and Crohn's disease leads to colon carcinogenesis.
- Hepatitis C in the liver predisposes to liver carcinoma.
- The Gram-negative bacterium H. pylori is a definite carcinogen for the development of gastric cancer and is the leading cause of stomach cancer.
- Chronic inflammation due to arthritis augments breast cancer metastasis.

Inflammatory Biomarkers and Cancer:

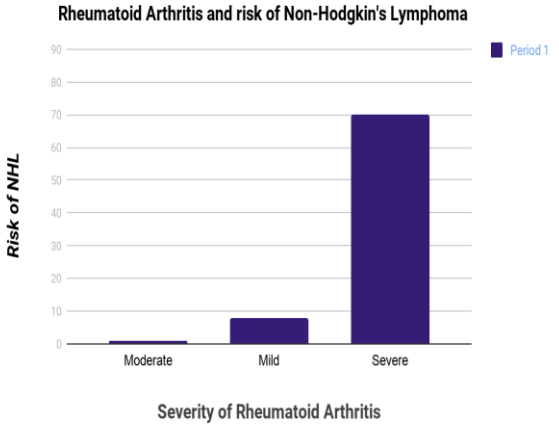
- Primary care patients with a raised inflammatory marker have an overall one-year cancer incidence of 3.53%, more than twice the risk in those with a normal test. Cancer incidence rises with rising levels of inflammatory markers and is higher still if a second test shows persistent raised inflammatory markers.
- In a recent meta-analysis of 12 prospective studies, elevated hs-CRP was associated with an increased risk of incident cancer of any type, lung cancer, and, possibly, colorectal, breast, and ovarian cancers, but not prostate cancer [2]
- A meta-analysis on the associations between circulating levels of C-reactive protein (CRP), interleukin 6 (IL6), tumor necrosis factor a (TNFa), and soluble TNF receptor 2 (TNFR2), and the risk of ovarian cancer provides evidence that elevated levels of CRP, but not circulating IL 6, TNFa, or soluble TNFR2, are significantly associated with an increased risk of ovarian cancer. These results suggest that circulating CRP may play a role in the etiology of ovarian cancer. [3]

Inflammatory Biomarkers and Cancer: Contd

- A study on the relationships between circulating levels of the inflammatory markers interleukin-6 (IL-6), C Reactive protein (CRP), and tumor necrosis factor-A (TNF-A) and total as well as site-specific cancer incidence identifies that:
  - Markers were more strongly associated with cancer death: hazard ratios were 1.63 (1.19-2.23) for IL-6, 1.64 (1.20-2.24) for CRP, and 1.82 (1.14-2.92) for TNF-A., these are only few of the many the markers in market.
  - All three markers were associated with lung cancer.
  - IL-6 and CRP were associated with colorectal cancer.
  - CRP was associated with breast cancer.
  - Also, these findings suggest that (a) the associations between IL-6, CRP, and TNF-A and the risk of cancer may be site specific and (b) increased levels of inflammatory markers are more strongly associated with the risk of cancer death than cancer incidence. [4]

Inflammatory Disease: Arthritis/COPD and Cancer

Originally it was thought that drugs used to treat rheumatoid arthritis patient could lead to cancer specifically Non- Hodgkin's lymphoma however, it has been shown by data that this is a false claim a study in Sweden confirmed this when there was no correlation between the drugs used to treat rheumatoid arthritis and a higher risk of developing lymphoma. In fact, when a further study was conducted the information in the graph was found.[6]



COPDs (Chronic Obstructive Pulmonary Disease) has shown correlation with lung cancer. COPDs like Chronic bronchitis or emphysema are major sources of inflammation in lung tissue and these conditions act as chances for the production of reactive oxygen species that may induce DNA damage and mutations and consequently become carcinogenic. [7]

Anti-inflammatory therapy for cancer treatment

- Targeted disruption of chronic inflammation should be addressed in the setting of established cancers – particularly as part of a combined therapeutic strategy – in order to yield more effective treatment options for patients; improving their quality of life and increasing overall survival. For example, the abrogation of inflammation in the Tumor-associated microenvironment (TME) may allow for additional successful clinical interventions that include chemotherapy, immunotherapy and/or radiotherapy. [1]

- The insights of tumour cells have co-opted some of the signalling molecules of the innate immune system, such as selectins, chemokines and their receptors for invasion, migration and metastasis. These insights are fostering new anti-inflammatory therapeutic approaches to cancer development. [2]

References

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