CANCER AND INFLAMMATION

REVIEW ON HOW INFLAMMATION FURTHERS TUMOUR DEVELOPMENT

Mar Bosch Queralt
Biomedical Sciences, Universitat Autònoma de Barcelona

UAB Universitat Autònoma de Barcelona

INTRODUCTION

The immune system normally causes an inflammatory reaction against cancer in order to kill the abnormal cells present in a tumour. However, there is increasing evidence that inflammation can also enhance tumour growth. The tumour cells have learnt to use the inflammatory process in a way that benefits their development.

METHODOLOGY

The first resource used was the book "The biology of cancer", by Weinberg, R.A. To complete the basement of the project, I performed a basic search on PubMed database in order to find the best reviews about cancer and inflammation. A research focused on finding both reviews and original articles centred on specific topics followed.

RESULTS

Evidences: inflammation can be protumorigenic

- **Many chronic inflammatory conditions predispose to certain types of cancer:** Not only is it proved that there are associations between inflammatory conditions and particular human tumours but also chronic inflammation has been linked to almost all steps in tumorigenesis.
- **Distinct populations of immune cells are detected in many cancers:** there is a leukocyte infiltrate in many tumours and the extent of it correlates with prognosis in some types of cancer.
- **Inflammatory cytokines are detected in many cancers:** high levels of cytokines and functional polymorphisms in cytokine genes have shown to be associated with poor prognosis. Levels of chemokines are associated with the inflammatory infiltrate and cell motility, and TNFα has shown to be directly transforming *in vitro*.
- **Long-term non-steroidal anti-inflammatory drug (NSAID) use protects from certain cancers:** long-term NSAID use decreases both the risk of some cancers and the mortality produced by them.
- **There is a link between genomic instability and inflammation:** signalling pathways involved in inflammation operate downstream of oncogenic mutations and inflammation induces somatic mutations which contribute to genomic instability.

Models: how is the relationship between cancer and inflammation described?

Inflammation is an enabling characteristic

Human tumours are characterized by a multistep development which allows them to acquire different biological capabilities that help them grow and invade tissues. Inflammation is understood as an enabling characteristic, which means that it enhances tumorigenesis and progression by helping incipient neoplasias acquire the hallmark characteristics that will promote their development.

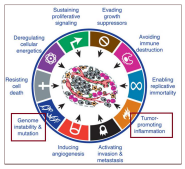


Figure: Biological capabilities and enabling characteristics (marked with squares).
From: Hanahan, D. & Weinberg, R.A. Hallmarks of Cancer: the next generation. *Cell* 144, 646-74 (2011)

Inflammation creates a phenocopy of the actions of an oncogene

Oncogenes confer a certain phenotype to the tumour cells, with traits that include loss of contact inhibition, gain of anchorage-independent growth and ability to proliferate more rapidly. Inflammation has been seen to also provide these traits by creating an environment full of cytokines, chemokines, growth factors and prostaglandins that affects all the cells found in it. Therefore, inflammation can be seen to be acting as a tumour promoter, like oncogenes do.

Tumours resemble wounds that fail to heal

There are striking parallelisms between the signalling processes used by tumour cells to progress and those used during wound healing. During wound healing, inflammation first enhances cell proliferation and then induces a resolution phase which stops the release of pro-inflammatory cytokines and growth factors. Therefore, the physiological inflammation is self-limiting. However, when proliferating cells are initiated cells that contain DNA damage, they continue to proliferate on expense of this environment rich in growth factors and inflammatory cells. In conclusion, tumour cells simply activate a normal pre-existing physiological program – wound healing – and exploit it in their favour.

Inflammation is a double-edged sword

Inflammation can also be understood as a double-edged sword. This means that while acute inflammation, which only lasts for a short period of time, is beneficial, chronic inflammation is proved to be harmful and lead to disease. As detailed in this review, many components of inflammation have been shown to enhance tumour development. However, complete blockade of inflammatory pathways has sometimes been proved to be harmful. Moreover, in the molecular level, one cytokine or transcription factor can have both tumour-promoting and tumour-antagonizing actions. Therefore, the balance between the tumour-promoting and tumour-antagonizing actions is what matters.

The cells

The tumour microenvironment is highly infiltrated by many leukocytes. These leukocytes are attracted by the increased constitutive level of cytokines and chemokines produced by tumour cells. Among all the cells that infiltrate a tumour, tumour associated macrophages are the ones that have the clearest tumour-promoting role.

T LYMPHOCYTES:
They are very abundant in the majority of human and experimental cancers and localise both within and around the tumour mass. Variable numbers of pro- and anti-tumour phenotypes. FOXP3+ Treg cells, CD4+ T cells and Th17 cells are a sign of poor prognosis.

B LYMPHOCYTES:
More often found adjacent to the tumour microenvironment. B cell infiltration normally associated with good prognosis though deposition can be tumour-promoting. Also some subtypes of B cells such as B10 or Breg cells are tumour-promoting.

NK AND NKT CELLS:
Usually found outside the tumour area. For some cancers they predict good prognosis.

Tumour-associated macrophages (TAMs)

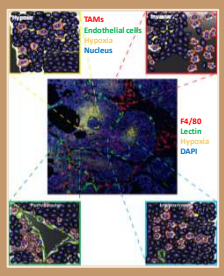


Figure: TAM localization within a tumour.
From: Ruffell, B., Affara. N.I. & Coussens, L.M. Differential macrophage programming in the tumour microenvironment. *Trends Immunol.* 33, 119-26 (2012)

Their phenotype progressively becomes tumour-educated: they switch from pro-inflammatory to a trophic immunosuppressive phenotype that promotes tumour progression and malignancy.

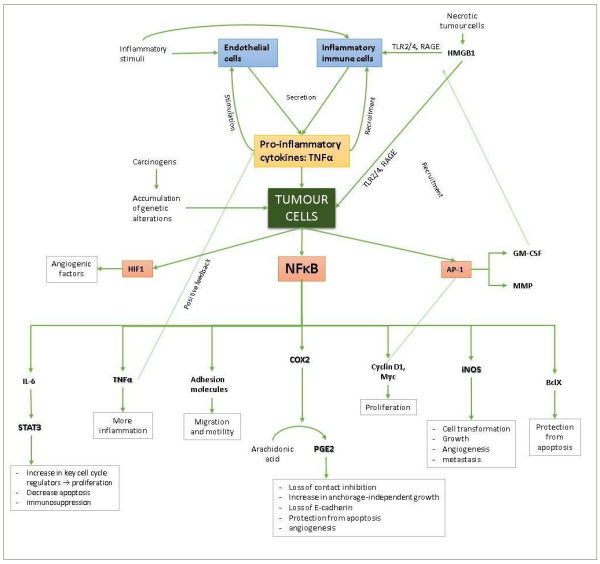
ANGIOGENESIS AND LYMPHANGIOGENESIS: hypoxic conditions attract TAMs and these activate HIF-1, which induces the expression of angiogenic and lymphangiogenic factors.

INVASION AND METASTASIS: TAMs enhance proliferation by a positive loop involving CSF-1 and CSF-1R which upregulates EGF expression. TAMs also modificate the extracellular matrix to allow the migration of tumour cells.

REPRESSING ACTIVITY OF Tc CELLS: TAMs secrete immunosuppressive cytokines and growth factors which prevent the action and recruitment of anti-tumorigenic cells.

The signalling pathways

The signalling pathways and the diverse components which are part of them provide the clearest molecular link between inflammation and cancer. In the following figure you can find a summary of all the components involved in the signalling pathways and how they interconnect with each other.



Inflammatory stimuli and necrotic tumour cells stimulate both immune and endothelial cells, which secrete pro-inflammatory cytokines.

These affect tumour cells, which activate signalling pathways normally involved in inflammation and initiate the transcription of many molecules which are beneficial for the development of the tumour.

Moreover, these signalling pathways are also activated downstream of genetic alterations or detection of damage-associated pattern molecules such as HMGB1.

Strategies used to modulate inflammation in order to prevent or cure cancer

- **NSAIDs:** they are associated with decreased colon-cancer incidence. They have been proved to be most effective during early stages of cancer development. However, important side effects need to be taken into consideration.
- **TLRs:** functional blockade using neutralizing antibodies or antagonists and TLR-signalling-pathway inhibitors.
- **STAT3:** it has also been pointed as an important target because it is a clear immunosupressor of the anti-cancer immune response.
- **TNFα:** TNFα antagonists are currently being tested in patients with advanced cancer.
- **Tumour microenvironment:** The many common features of the different tumour microenvironments suggest that targeting their cells or their communications could have applications across different tumour types. Some examples are to eliminate or reprogramme myeloid cells or to use tyrosine kinase inhibitors that impact on VEGF signalling pathways, which promote angiogenesis.

It is particularly difficult to know whether inflammation in a particular tumour has anti or pro-tumour actions, since inflammatory mediators can have many different effects depending on the context in which they are called into play. Nevertheless, the knowledge gained in understanding the cancer-related inflammation is now finally being translated into clinical trials.

CONCLUSION

Cancer is an extremely complex disease that takes advantage from the normal physiology of the human body and converts it into pathological states. The inflammatory process is not an exception: it is clear now that the cells and the signalling pathways normally involved in inflammation can function to further tumour growth and development when influenced by the presence of tumour cells surrounding them.
Even though cancer-related inflammation is still not totally understood, it is sure that it is an important player in the development of cancer. Therefore, it must be taken into account when approaching cancer and opens new doors to both the prevention and treatment of this disease.