MALIGNANT PLEURAL MESOTHELIOMA
AND
INFLAMMATION

INTRODUCTION

Tumours are characterised by a series of **genetic anomalies** with a **proliferative potential** that leads to **cellular transformation**.

Nevertheless, it is believed that the micro-environment that surrounds the tumour (**tumour micro-environment or TME**) may also have an important role in the fate of tumour cells, acting on the cellular progression or regression.

The correlations which exist between **cancer and inflammation** have been documented since 1863, when Virchow observed that tumour tissue is often surrounded by inflammatory cells which are discovered in the analysis of bioptic samples[i].

In immunodeficient mouse models, it has been demonstrated that inflammation may precede the development of **malignant mesothelioma**[ii]. Moreover, epidemiological studies have revealed that chronic inflammation caused by chemical or physical agents and the inflammatory and autoimmune reactions of uncertain origin predispose people to certain types of tumours [iii iv].

Growing evidence shows that the "inflammation-cancer" connection is not only limited to initial processes of tumour development; in fact, all types of cancers would seem to have an **active inflammatory component in** their **micro-environment**. These experimental and clinical observations lead to a greater confirmation that inflation related to cancer may be one of the main typical characteristics of neoplasias itself[v].

INFLAMMATION

One of the main factors that characterise the tumour micro-environment is **persistent chronic inflammation**[vi].

Tumour-related inflammation is mainly triggered by innate immunity cells (especially **macrophages**), which are present in large quantities in the tumour micro-environment, but it is also

maintained by stromal cells, such as fibroblasts, by blood vessel cells or by the same tumour cells[vii].

Two **pathogenic ways correlate cancer and inflammation.**

The *intrinsic way* is guided by genetic alterations that cause neoplasias. For example, these genetic modifications may lead to the triggering of various types of oncogenes, to mutation, to rearrangement or to chromosomal amplification, or they may make oncosuppressor genes inactive, which initiate an inflammatory process inside the neoplastic cell.

The *extrinsic way*, on the other hand, is mediated by inflammatory cells of the innate immunity; we are talking mainly of macrophages.

These two inflammatory paths join the activation of transcription factors, such as the NF-.B, of signal transducers, of transcriptional activators 3 (STAT3) and of the hypoxia-inducible factor 1 (HIF1).

In the past ten years, the mechanisms through which chronic inflammation supports tumour growth have been further delved into. Different soluble **inflammatory mediators**, either produced by macrophages or by tumour cells, act as growth factors that directly stimulate the proliferation of tumour cells and increase their resistance to apoptotic stimuli. These include, for example, the primary inflammatory cytokines IL-1 and TNF, which activate NF-kB, the key regulator of the inflammatory response.

In tumour cells, **NF-kB** activates the expression of anti-apoptotic genes (for example, c-IAP, BCL2, c-FLIP) and of genes that regulate cellular proliferation (for example, Cyclin, c-Myc).

In the macrophages, NF-kB activates different genes that encode for cytokines (Egil-1, TNF, IL-6), chemokines (i.e., CCL2, CCL5, CXCL8) and reactive enzymes (for example, COX-2), which further stimulate the inflammatory response, thus amplifying the recruitment of new inflammatory cells in the tumour.

Cytokine **IL-6** activates transcription factor STAT3, another important inflammation and tumour development regulator. In tumour cells, STAT3 stimulates cellular survival and proliferation, whilst in the macrophages its persistent activation leads to immune suppression.

Besides, little is known about the mechanisms that lead to tumour initiation within the context of chronic inflammation. There is evidence that inflammatory mediators such as **cytokines**, **reactive oxygen species** (ROS) and **reactive nitrogen species** (RNS) lead to epigenetic alterations in pre-cancerous cells, cause the silencing of onco-suppressor genes and the inhibition of DNA repairing mechanisms[viii]. Certain inflammatory cytokines and other mediators increase the survival of tumour cells, the motility and invasiveness, also encouraging the angiogenic capacity, which is crucial for allowing oxygen, nutrients and growth factors to reach tumour cells[ix x].

In this way, chronic inflammation favours the accumulation of **DNA mutations** and increases the proliferation potential of the cells. It is believed that this cancerogenesis process induced by

inflammation may require several years, as a consequence of a lack of balance between continuous casual mutations and DNA repair, cellular death and cellular proliferation, recognition or escape from control of the immune system.

While in the past 15 years incredible progress has been made in terms of understanding the mechanisms through which cancer-related inflammation might have a negative impact on tumour progression, little is known to this day with regards to the **effects of chronic inflammation on cancerogenesis**. It is believed that long-term exposure to inflammatory mediators (cytokines, reactive oxygen and nitrogen species) causes genotoxic damage to the DNA, constantly putting pressure on the DNA repair system. Cells where the DNA repair response is inhibited or is less efficient are at high risk of genomic instability and are more predisposed to malignant transformation. At present, little is known about the mechanisms underlying these processes.

MACROPHAGES ASSOCIATED WITH TUMOURS

Macrophages associated with tumours (TAM) are innate immunity cells that are abundantly present in tumours. They are key initiators of the persistent inflammation present in the tumour micro-environment (TME), since they are the main producers of reactive mediators that perpetuate and amplify the inflammatory cascade[xi] [xii].

A typical characteristic of macrophages is their **functional plasticity**. In fact, the acquisition of their various functions is precisely dictated by specific local stimuli that activate separate functional processes: actually, they are not only able to fight the onset and progression of the tumour but also lead to the start of the tumour as well[xiii].

Macrophages can be classified, in a simplistic way, as **M1** or classic macrophages, having the tumour-suppressor phenotype and capable of product large quantities of inflammatory cytokines and **M2,** or alternative macrophages that have the immune-suppressor phenotype and control the trophic activity of tissues as well as the angiogenesis[xiv] [xv] [xvi].

Macrophages perform many actions aimed at encouraging **tumour progression**: they produce growth and survival factors for tumour cells and the vascularisation (neoangiogenesis), they contribute to the deterioration of the extracellular matrix and to the remodelling, they facilitate the invasion of tumour cells and the metastasis, and they produce immunity mediators that suppress anti-tumour activity[xvii] [xviii].

Consequently, the quantity of TAM in most solid and haematological tumours has been associated with an **unlucky prognosis and resistance to therapies**[xix].

The TAMs have a limited cytotoxic action against neoplastic cells and, according to certain studies,

it appears that they are in fact capable of encouraging tumour proliferation, the deterioration of the extra-cellular matrix and the ability to elude the control of the immune system[xx xxi xxii xxiii xxiv].

Moreover, the presence of TAMs in tumour tissue is associated with the **quick rate of progression**[xxv xxvi]. Hence, macrophages constitute a source of inflammatory mediators at the tumour level. This also occurs for MPM, although it has been reported in literature that the mesothelial cells of the pleura are also capable of **producing reactive mediators** in response to asbestos fibres.

On the basis of functional activities and gene expression profiles, some researchers have demonstrated that TAMS are polarised macrophages M2[xxvii]. Moreover, TAMs have been characterised in various mouse tumour models, and the inflammatory paths that are involved the most in the pro-tumour activity have been defined[xxviii xxix].

In recent years, great emphasis has been placed in identifying macrophages at the tumour site for **therapeutic purposes**. Moreover, it has been demonstrated that inhibiting these cells in experimental contexts would limit tumour growth and metastatic spreading[xxx]. Inhibiting the recruitment of monocytes at the tumour sites, in combination with chemotherapy, appears to significantly increase the efficacy of the therapeutic treatment in mice with tumours. This is probably due to the fact that the presence of TAMs and myeloid cells is also strongly implicated in the ineffectiveness of anti-tumour therapies[xxxi xxxii xxxiii]. Recent clinical studies have also provided interesting results, through the use of inhibitors that limit the action of the chemokines[xxxiv].

PLEURAL MESOTHELIOMA

Pleural mesothelioma is a pathological condition characterised by chronic persistent inflammation. It is a very aggressive tumour caused by the **neoplastic transformation of the mesothelial cells** that line the body's serous cavities and internal organs; in 80% of the cases it is of pleural origin and it is defined as malignant pleural mesothelioma (MPM)[xxxv]. MPM is usually discovered in the **advanced stage**, since there are no markers that allow early diagnosis[xxxvi]. Malignant mesothelioma is almost insensitive to current chemotherapy, and still has a very limited global survival rate.

It is a highly malignant disease associated with long-term exposure to **asbestos or other particulate fibres**[xxxvii]. In fact, its incidence is strongly linked to exposure to airborne asbestos fibres[xxxviii]. Once the asbestos enters the lungs, the macrophages are locally recruited and activated in an attempt to eliminate the fibres, but they are unable to carry out this "clean up" due to the non-degradable nature of asbestos. This failed deterioration of asbestos fibres by the macrophages leads

to a state of **chronic inflammation** and to a fibrogenic response by the fibroblasts, which in the long term facilitates the transformation of healthy pleural cells into tumour cells[xxxix xl xli xlii].

Hence, the inhaled fibres are not degradable, and they cause a persistent local state of inflammation. Due to the volatile nature of particulate fibres, the people who work directly with asbestos are not the only ones at risk, as entire populations who live in areas where asbestos was present may also be affected. Therefore, it is possible to state that malignant mesothelioma is a tumour that is certainly related to chronic inflammations[xliii].

Genetic anomalies tied to MPM have been widely studied. In fact, a wide range of genetic mutations has been identified, including, for example: BAP1, CDKN2A, Ras, Wnt, p16, TP53, SMACB1, NF2, PIK3CA[xliv xlv xlvi].

This wide spectrum of genetic mutation indicates that the anomalous proliferation of the neoplastic cells is not caused by the oncogenic activity of one or of some oncogenes, as it happens in many types of tumours (for example, KRAS and pancreatic or lung cancer, BRCA1 and breast cancer)[xlvii xlviii]. In this case, we are dealing instead with the result of casual damage to the DNA, due to an upstream condition (for example, long-term inflammation), confirming that inflammation is indeed one of the main causes of carcinogenesis[xlix l].

It is known that certain polymorphisms of genes related to inflammations cause a predisposition to the disease. For example, SNPs in Toll-like receptors have been found to be related to infections and chronic inflammatory diseases[li]. For example, the SNPs of gene NLRP3 appear to be related to susceptibility to the HIV virus, to Crohn's Disease, to rheumatoid arthritis and to diabetes[lii liii liv]. Girardelli et all have demonstrated that in patients suffering from MPM, the SNPs in gene NLRP1 are more frequent[lv].

Several studies have reported the expression of **inflammatory mediators** in MPM[lvi lvii lviii]. Hegmans JP et all have demonstrated that the inflammatory cellular infiltrate of MPM is full of macrophages, thus implying that these cells play a crucial role in the biology of the mesothelioma[lix].

It is well known that asbestos fibres cause the inflammatory sublayer[lx lxi]. The recruitment of the macrophages is also induced by the adipocytes involved in the inflammation caused by the presence of asbestos. In fact, some researchers have demonstrated that adipocytes exposed to asbestos fibres are capable of producing inflammatory cytokines (IL6 and CCL2), which in turn draw and recruit macrophages in the inflammatory micro-environment.

However, at present a complete characterisation of the inflammatory paths involved in MPL is still not available.

CONCLUSIONS

Inflammation is present in the **micro-environment that surrounds the tumour tissue** and, probably, it is not simply a cellular characteristic surrounding the neoplasias, but instead appears to be and active component involved in the carcinogenesis.

Several studies aim to study the mechanisms that lead to the neoplastic transformation of various neoplasias and, among these, of **mesothelioma,** focusing on the inflammatory response.

Researchers are currently attempting to understand which inflammatory paths are most involved in the onset and progression of mesothelioma, and if there are specific characteristics that can explain why the selected individuals develop the disease.

It would be crucial to identify **subjects at a high risk** of developing mesothelioma, and to find out more about chronic inflammation and its **capacity to create a predisposition to carcinogenesis**.

This research may lead to the discovery of **new molecular targets** useful for therapy or for prevention drugs[lxii].

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