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Stromal inflammation, fibrosis and cancer: an old intuition with promising potential

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Abstract

It is now well established that the biology of cancer is influenced by not only malignant cells but also other components of the tumour microenvironment. Chronic inflammation and fibrosis have long been postulated to be involved in carcinogenesis. Chronic inflammation can promote tumorigenesis *via* growth factor/cytokine-mediated cellular proliferation, apoptotic resistance, immunosuppression; and free-radical-induced oxidative DNA damage. Fibrosis could cause a perturbation in the dynamics of the tumour microenvironment, potentially damaging the genome surveillance machinery of normal epithelial cells. In this review, we will provide an in-depth discussion of various diseases characterised by inflammation and fibrosis that have been associated with an increased risk of malignancy. In particular, we will present a comprehensive overview of the impact of alterations in stromal composition on tumorigenesis, induced as a consequence of inflammation and/or fibrosis. Strategies including the application of various therapeutic agents with stromal manipulation potential and targeted cancer screening for certain inflammatory diseases which can reduce the risk of cancer will also be discussed.

INTRODUCTION

In recent years, there is growing consensus that the biology of cancer is not solely defined by malignant cells, but also by the surrounding tumour microenvironment (TME). The TME consists of cellular and non-cellular stroma. The concept that the TME

may influence cancer biology was inspired by the observation of immune cells surrounding the tumour by Rudolf Virchow in 1863, and "the seed and soil theory" by Stephen Paget in 1889, in which he hypothesised that the metastatic destination of a certain cancer is dependent on similarities between the TME of primary tumour and the microenvironment at the site of metastases.[1,2] Since then, there have been significant advancements in the understanding of the impact of the TME on the behaviour of malignant cells, from initial tumorigenesis, through progression to therapy resistance.[3-5] This review will focus on the impact of both the physiological and pathological tissue microenvironment, particularly stromal fibrosis and inflammation, on tumorigenesis.

In this context, stroma refers to the component of an organ which provides biomechanical and nutritional support to the corresponding parenchyma. Specifically, it comprises of immune cells, fibroblasts, mesenchymal stromal cells, endothelial cells, pericytes, adipocytes, and the extracellular matrix (ECM). The ECM, consisting of collagen, proteoglycans, glycosaminoglycans and other macromolecules, provides structural and biochemical support for cellular components in the surrounding parenchyma. Of note, some authors do not include immune cells as a component of stroma, however, immune cells such as macrophages, neutrophils and lymphocytes, play an integral role to the function of parenchymal cells and can have far-reaching effects on tumour biology and consequent behaviour, as such they will be classified as a stromal component in this review.

Many stromal components have been shown through various *in vitro* and animal studies to influence the behaviour and fate of normal cells, including altering the risk of malignant transformation.[6-8] Inflammation and fibrosis are both common processes that significantly alter the cellular and ECM components of normal stroma and so may influence or underlie such behavioural shifts. Both processes have been seen to upregulate the expression of several tumorigenic signalling pathways including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), signal transducers and activators of transcription (STAT), wingless-related integration site (Wnt) and phosphatidylinositide 3-kinase (PI3K) *via* the release of pro inflammatory cytokines[9-12].

Hence, several inflammatory and fibrotic conditions have been linked as triggers for tumour development in the organ involved, whether due to autoimmune responses (inflammatory bowel disease and colorectal cancer[13]), bacterial or viral infections (pneumonia or tuberculosis with lung cancer[14]) and environmental factors (silica and lung cancer[15]).

Often, these pathological processes appear to be required for tumorigenesis rather than simply an overrepresentation of certain otherwise normal stromal components. For instance, inflamed adipose mammary tissue in the context of obese mice, increases myofibroblasts number, promoting fibrosis and transformation of normal to malignant breast tissue[6] , whereas normal mouse fibroblasts have been shown to prevent clonal proliferation of polyoma virus-transformed cells in vitro.[7] However, there are less frequent precedents where normal stromal components may also contribute to tumorigenesis. Normal fibroblasts have been demonstrated to promote the generation of breast cancer stem cells.[8] Additionally, high mammographic breast density, which results from a higher density of stromal and glandular breast components and a lower proportion of adipocytes, is a potent risk factor for breast cancer development.

In this review we will discuss various medical conditions substantively characterised by inflammation and fibrosis, specifically those known to be linked to increased cancer risk. Furthermore, we will look to whether scenarios exist where physiological variations in stromal composition correlate with differing cancer incidence. In doing so, we will discuss the biological contribution of the various stromal components to tumorigenesis known to date and discuss interventions that may influence these processes to achieve therapeutic advantage.

CONCLUSION

In conclusion, the correlation between chronic inflammation, fibrosis and cancer risk is complex, with the former being more straightforward. Chronic inflammation in the stroma of different body tissues promotes carcinogenesis *via* different mechanisms –

growth factor/cytokine-mediated cellular proliferation, apoptotic resistance and immunosuppression; and free-radical-induced oxidative DNA damage. However, certain immune cells, involved in tumour-surveillance may be depleted, as seen in IPF and hepatic cirrhosis, thereby raising cancer risk by compromising immune surveillance of tumours. The relationship between stromal fibrosis and cancer risk varies in different organs, implying that the effects of fibrosis could be tissue-specific. Increased stromal fibrosis is associated with an increased cancer risk in organs like the lung, liver, biliary tract and colorectal region. Conversely, in other organs such as pancreas and potentially, oesophagus, increased stromal fibrosis may confer a lower cancer risk.

At this current time, the mechanism by which fibrosis influences cancer risk is still ambiguous. We propose two hypotheses. Firstly, a fibrotic environment contributes to an aberration in ECM dynamics which affects normal cellular behaviour and ultimately neoplastic transformation. Secondly, we hypothesise that fibrosis may present as a safe alternative to cellular regeneration which has the potential to produce aberrant DNA mutations, resulting in tumour formation. What determines the former or the latter are a multitude of factors which could include fibroblast heterogeneity and plasticity; extent of fibrosis; inflammation; and the predominance of certain mediators over others. Therefore, future studies, especially in-vitro and animal studies, should investigate the mechanisms by which fibrosis contributes to carcinogenesis in various organs in further depth and determine if fibrosis, alone or only in conjunction with inflammation would promote carcinogenesis. Furthermore, the role of surveillance screening and therapeutic agents with stroma manipulation potential in patients with diseases which involve chronic inflammation and fibrosis should be further studied to reduce the incidence of relevant cancers.

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