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Mini-review

Hepatocellular carcinoma: Mouse models and the potential roles of proteases

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ABSTRACT

Primary liver cancer is the second most common cause of mortality from cancer. The most common models of hepatocellular carcinoma, which use a chemical and/or metabolic insult, xenograft, or genetic manipulation, are discussed in this review. In the tumour microenvironment lymphocytes, fibroblasts, endothelial cells and antigen presenting cells are important determinants of cell fate. These cells make a range of proteases that modify the biological activity of other proteins, particularly extracellular matrix proteins that alter cell migration of tumour cells, fibroblasts and leucocytes, and chemokines that alter leucocyte migration. The DPP4 family of post-proline peptidase enzymes modifies cell movement and the activities of many bioactive molecules including growth factors and chemokines.

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Hepatocellular carcinoma

Hepatocellular Carcinoma (HCC) is responsible for 70–85% of primary liver cancer cases [1]. It is the fifth most common malignancy and the second leading cause of cancer-related mortalities worldwide [2,3]. Globally, rates are more than twice as high in males than females [1]. Furthermore, it has been shown that the mortality from HCC has been increasing, whilst mortalities from other cirrhosis based conditions are decreasing [4].

There are many risk factors associated with liver cancer including Hepatitis B and C infections, exposure to Aflatoxin B1, along with alcohol related cirrhosis and non-alcoholic fatty liver disease associated with obesity [1,5–7]. Thus there is an urgent need for research to improve both diagnosis and treatments of hepatocellular carcinoma. However, given the complexity of both the disease and the diverse risk factors, there are advantages to employing models that reflect both the HCC and the environment in which they form. There are three overall model types currently used for the study of HCC in mice and rats: chemically induced, genetic and xenograft models. HCC models in use generally combine two or more model types as liver injuries generally synergise.

The tumour microenvironment in HCC

Cancer was viewed as a cell-autonomous process, in which the acquisition of mutations in oncogenes and suppressor genes leads to increased proliferation and decreased cell death. It is now known that carcinomas are complex organs consisting of a variety of cells that promote tumour growth and protect it from the immune system [8]. The tumour microenvironment refers to the range of non-malignant cells in a tumour including endothelial cells and their precursors, pericytes, fibroblasts of various phenotypes including myofibroblasts, mast cells, T, B, natural killer (NK) lymphocytes, and antigen presenting cells such as macrophages and dendritic cells [9] (Fig. 1). The importance of the tumour microenvironment in carcinogenesis was originally proposed in 1889 by Paget in his seed and soil hypothesis, in which circulating cancer cells do not simply grow where they are seeded in the body, but rather their fate is determined by the microenvironment of the seeded tissue. The tumour microenvironment defines the behaviour of the tumour, not by the genetics and phenotype of the tumour cells alone but by the interactions and influences of surrounding cells. It is now apparent that cross-talk between tumours and the tumour microenvironment is crucial for cell survival, growth, proliferation, epithelial–mesenchymal transition (EMT) and metastasis [10,11]. Given the complex risk factors and progression of HCC, an understanding of the key players is crucial.

Fibroblasts

Fibroblasts are the non-vascular, non-epithelial, non-inflammatory cells of the connective tissue and are its main component [12,13]. They are embedded within the fibrillary matrix and are largely

Abbreviations: CAF, cancer associated fibroblasts; DEN, diethylnitrosamine; DPP, dipeptidyl peptidase; ECM, extracellular matrix; EGF, epidermal growth factor; EMT, epithelial–mesenchymal transition; FAP, fibroblast activation protein; FGF, fibroblast growth factor; HCC, hepatocellular carcinoma; HFD, high fat diet; HSC, hepatic stellate cells; MMP, matrix metalloproteinase; NMDA, N-nitrosodiethylamine; PB, phenobarbital; TAA, thioacetamide; TAM, tumour associated macrophages.

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responsible for its synthesis. Cancer associated fibroblasts (CAF) are the most prominent cell type within the tumour stroma of many cancers and play a critical role in tumour–stroma interactions [12]. They express alpha-smooth muscle actin (α-SMA), vimetin, desmin and fibroblast activation protein (FAP) [14].

CAFs promote tumourigenesis and are involved with growth and invasion [15]. They are able to produce a range of inflammatory and tumourigenic mediators such as epidermal growth factor (EGF), fibroblast growth factor (FGF), IL-6, and the chemokines chemokine (C–X–C motif) ligand 12 (CXCL12), matrix metalloproteinase (MMP)-3, and MMP-9 [15]. Injection of either normal or transformed fibroblasts has been shown to enhance the tumourgenicity of several different human cancer cell lines in xenograft experiments [16]. Fibroblasts from reactive stromal regions of tumours have the capacity to transform otherwise non-malignant epithelial cells [17,18]. In co-cultures of CAFs with squamous cell carcinoma (SCC) cells the leading cells in tumour invasion are CAFs, whilst the cancer cells move into the extracellular matrix (ECM) behind them [19]. Some CAFs also possess an ability to suppress the immune system [20].

Hepatic stellate cells

Hepatic stellate cells (HSCs) are a key mediator of progressive liver fibrosis [21]. HSCs are normally quiescent but in response to chronic liver injury become activated. During this activation the HSCs trans-differentiate into myofibroblast-like cells and this is seen as a crucial event in the development of liver cirrhosis [22]. Activated HSC can infiltrate the stroma of the liver and localise around tumour sinusoids, fibrous septa and capsules [23,24]. It has been shown that the co-culture of HCC cells with HSCs promotes HCC cell migration, and invasion via the FAK-MMP9 signalling pathway [25]. Co-cultures with HSC-HCC induce HSC proliferation, migration and expression of proangiogenic genes such as vascular endothelial growth factor (VEGF) and MMP-2.

Tumour-associated macrophages (TAMs)

Tumour associated macrophages are located in the tumour stroma and can undertake a wide range of polarised activation states ranging from classically activated (M1), which produce type 1 pro-inflammatory cytokines and play an anti-tumourigenic role, to alternatively activated (M2), which produce type 2 cytokines and promote both an anti-inflammatory response and pro-tumourigenic activity [26].

Alternatively activated (M2) macrophages with pro-tumourigenic phenotypes have been well documented in cancers other than HCC. M2 macrophages appear to contribute to poor prognosis in human HCC through CCL2-induced EMT [27]. Recently, numerous studies have shown a clear role for TAMs in supporting multiple aspects of tumour progression. The Kupffer cells, which are liver specific macrophages, are able to impair CD8+ T cell dependent immune responses through the interaction between Programme death 1 (PD1) on CD8+ T cells and PD ligand-1 (PD-L1), causing a deficiency of CD8+ T cell cytotoxic function in HCC [28,29].

Proteases

Proteases have fundamental roles in all major biological processes, and are associated with a wide variety of pathological conditions including cancer [30]. Tumour cell invasion occurs when tumour cells attach themselves to the underlying basement membrane, then local proteolysis precedes tumour cell migration through the proteolytically modified region [31]. Whilst proteases have been shown to play crucial roles in this process, it has now become apparent that they also have important roles in other processes in tumours, such as tumour growth, angiogenesis and reducing cell death. One of such protease family is the matrix metalloproteinases family (MMP), which consists of 23 human enzymes that are able to degrade the ECM. As such they have been associated with metastasis and invasion in cancers. However, recent studies have found that certain MMPs can also provide a protective effect against cancers at certain stages [30]. MMP9 and MMP2 are critical for the invasive potential of several tumours including HCC [32,33]. Here we review a serine protease family, the DPP4 family, and its possible roles in tumours.

DPP4 gene family

The dipeptidyl peptidase 4 (DPP4) gene family consists of four atypical serine proteases: DPP4, fibroblast activation protein (FAP), DPP8, and DPP9. These proteins are active as dimers or tetramers

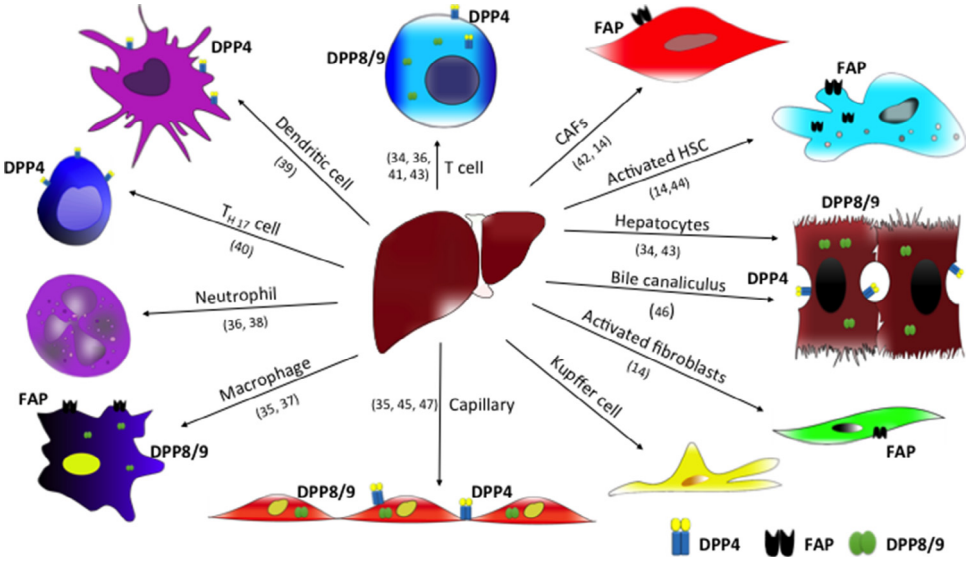

Fig. 1. Cartoon illustrating major liver cell types that may interact with a tumour. The locations of proteases of the DPP4 family are illustrated, along with references. CAF, carcinoma-associated fibroblasts; DPP4, dipeptidyl peptidase 4; DPP8/9, dipeptidyl peptidase 8/9; FAP, fibroblast activation protein; HSC, hepatic stellate cell; $T_{H\ 17}$, T helper cell type 17. Numbers in brackets are references.

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