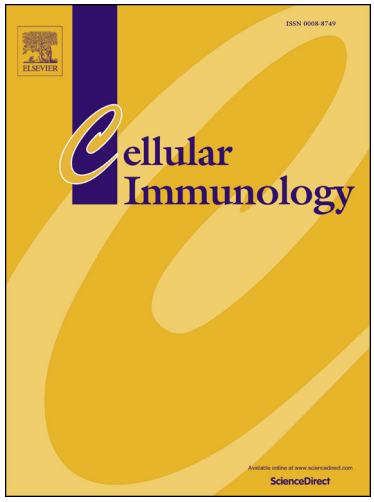

Research paper

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PII: S0008-8749(18)30142-4
DOI: https://doi.org/10.1016/j.cellimm.2018.03.010
Reference: YCIMM 3786

To appear in: *Cellular Immunology*

Received Date: 21 October 2017
Revised Date: 12 March 2018
Accepted Date: 29 March 2018

Please cite this article as: J. Keirsse, H. Van Damme, X. Geeraerts, A. Beschin, G. Raes, J.A. Van Ginderachter, The role of hepatic macrophages in liver metastasis, *Cellular Immunology* (2018), doi: https://doi.org/10.1016/j.cellimm.2018.03.010

The role of hepatic macrophages in liver metastasis

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Abstract

The liver is a major target organ for metastasis of both gastrointestinal and extra-gastrointestinal cancers. Due to its frequently inoperable nature, liver metastasis represents a leading cause of cancer-associated death worldwide. In the past years, the pivotal role of the immune system in this process is being increasingly recognised. In particular, the role of the hepatic macrophages, both recruited monocyte-derived macrophages (Mo-Mfs) and tissue-resident Kupffer cells (KCs), has been shown to be more versatile than initially imagined. However, the lack of tools to easily distinguish between these two macrophage populations has hampered the assignment of particular functionalities to specific hepatic macrophage subsets.

In this Review, we highlight the most remarkable findings regarding the origin and functions of hepatic macrophage populations, and we provide a detailed description of their distinct roles in the different phases of the liver metastatic process.

Keywords

liver metastasis; hepatic metastasis; Kupffer cell; hepatic macrophage

Introduction

Metastasis – the dissemination of cancer cells from a primary tumour to other sites in the body - is the major cause (>90%) of cancer-associated death [1,2]. More specifically, metastasis to the liver is a common event in multiple cancer types and is a leading cause of death in gastrointestinal cancers, including colon cancer and pancreatic cancer, but also melanoma and breast cancer [3]. In the specific case of colorectal carcinoma, liver metastasis has been reported in approximately 25% of patients upon primary tumour diagnosis and in another 40-50% of

APC; Antigen presenting cell, BM; Bone Marrow, CCL; CC-chemokine ligand, CEA; Carcinoembryonic antigen, CEAR; Carcinoembryonic antigen receptor, Clec4f; C-Type Lectin Domain Family 4 Member F, CRC; Colorectal cancer, CTC; Circulating tumour cell, CXCL; chemokine (C-X-C motif) ligand, DC; Dendritic cell, ECM; Extracellular matrix, EGF; Endothelial growth factor, EGFR; Epidermal growth factor receptor, FL; Foetal liver, GM-CSF; Granulocyte-macrophage colony-stimulating factor, HGF; Hepatocyte growth factor, HStC; Hepatic stellate cell, ICAM; Intercellular adhesion molecule, IFN; Interferon, IL; Interleukin, KC; Kupffer cell, LSEC; Liver sinusoidal endothelial cell, M-CSFR; Macrophage colony-stimulating factor receptor, mAb; monoclonal antibody, MHC; Major histocompatibility complex, MIF; Macrophage migration inhibitory factor, MMP; Metalloproteinase, Mo-DC; Monocyte-derived dendritic cell, Mo-Mf; Monocyte-derived macrophage, NK; Natural killer, NO; Nitric oxide, PDAC; Pancreatic ductal adenocarcinoma, ROS; Reactive oxygen species, TEM; Transendothelial migration, TGF; Transforming growth factor, TLR; Toll-like receptor, TNF; Tumour necrosis factor, VCAM; Vascular cell adhesion molecule, VEGF; Vascular endothelial growth factor, YS; Yolk sac.