

Matrix metalloproteinase-9: A deleterious link between hepatic ischemia-reperfusion and colorectal cancer

Sébastien Lenglet, François Mach, Fabrizio Montecucco

Sébastien Lenglet, François Mach, Fabrizio Montecucco, Cardiology Division, Department of Medicine, Geneva University Hospital, Foundation for Medical Research, 1211 Geneva, Switzerland

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Correspondence to: Dr. Fabrizio Montecucco, MD, PhD, Cardiology Division, Department of Medicine, Geneva University Hospital, Foundation for Medical Researches, 64 Avenue Roseaie, 1211 Geneva,

Switzerland. fabrizio.montecucco@unige.ch

Telephone: +41-22-3827238 Fax: +41-22-3827245

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Abstract

Despite the advent of improved surgical techniques and the development of cytotoxic chemotherapeutic agents useful for the treatment of colorectal cancer, the primary clinical challenge remains that of preventing and combating metastatic spread. Surgical resection is the best treatment for colorectal metastases isolated to the liver. However, in rodent models, the hepatic ischemia-reperfusion (I/R) applied during the surgery accelerates the outgrowth of implanted tumors. Among the adverse effects of I/R on cellular function, several studies have demonstrated an over expression of the matrix metalloproteinase-9 (MMP-9) in the ischemic liver. Since several studies showed high local levels of expression and activity of this proteolytic enzyme in the primary colorectal adenocarcinoma, the role of MMP-9 might be considered as a potential common mediator, favoring both growth of local tumor and the dissemination of colorectal carcinoma metastases.

INTRODUCTION

Colorectal cancer is one of the most commonly diagnosed cancers in developed countries and it is ranked as the second leading cause of death among cancer patients^[1]. The majority of these cases is sporadic and develops from a precursor lesion, the adenomatous polyp. At the diagnosis, colorectal cancer is localized to the colon (Dukes A and B stages) in 54% of cases, while it is metastatic to lymph nodes and distant organs (Dukes C and D stages) in the remaining 46%. The survival data demonstrate that the prognosis depends on the severity of the disease: around 80% of patients have long term survival with node negative disease (Dukes A and B stages), this percentage drop to 4% for 5-year survival in patients with metastases (Dukes D stage)^[2]. The liver is the most frequent metastatic site of colorectal cancer, and the complete surgical resection of isolated metastases in this organ has been shown to improve disease outcomes^[3]. Unfortunately, this therapeutic procedure does not avoid a high rate of metastasis recurrence within the

liver. Experimental evidence accumulated over the last two decades has suggested the association between the increase risk of metastatic relapse and their surgical resection in the liver. Indeed, besides the presence of residual or dormant malignant cells, the blood loss incurred during the operation disseminates colon cancer cells into the peripheral blood^[4]. In order to limit the blood loss during the parenchymal resection, surgeons occlude the inflow of blood to the liver.

HEPATIC ISCHEMIA-REPERFUSION INJURY

However, hepatic ischemia-reperfusion (I/R) is an additional and strong stimulus that promotes the outgrowth of micrometastases in the liver^[5]. Local response to I/R is quite complex, but it can be classified into two distinct phases. The acute hepatocellular injury is caused by reactive oxygen species, intracellular and mitochondrial Ca²⁺ overload, complement activation and release of cytotoxic cytokines, and is reflected by a rise in plasma liver enzymes. The late phase is characterized by neutrophil infiltration causing further damage to the parenchyma, mainly through a protease-dependent pathway^[6,7].

In a mouse model of colorectal liver metastases, van der Bilt and colleagues have demonstrated that intermittent clamping prevents both early and late hepatocellular damage and I/R-accelerated tumor growth^[8]. These results might be associated with the reduction of neutrophil infiltration in the parenchyma, which contributes to tumor growth by producing proliferation and angiogenesis-stimulating factors and cytokines^[8].

METALLOPROTEINASE 9 AND COLORECTAL CANCER

Numerous publications have demonstrated that the disease progression in animal models of tissue invasion and metastasis correlate with enhanced secretion of MMPs by tumor and/or stromal cells. Indeed, the metastatic cascade is characterized by the stromal invasion, “intravasation” of the circulatory system at the primary site, “extravasation” at the secondary site and outgrowth of new tumors. These progressive steps require degradation of the extracellular matrix components by proteolytic enzymes, such as matrix metalloproteinases (MMPs)^[9]. Increased expression of various isoforms (MMP-1, -2, -3, -7, -9, -12, -13) has been also related with the pathophysiology of the transformation of human neoplastic colorectal mucosa to adenomatous polyps, invasive colorectal cancers, and metastases^[10]. Among different MMPs, MMP-9 is of particular interest. Indeed, MMP-9 (also known as gelatinase B) is the main enzyme responsible for the degradation of type IV collagen (a major component of basement membranes) and the denatured collagens (gelatins). Importantly, this capacity of MMP-9 has been previously associated with colorectal cancer progression and dissemi-

nation of metastasis^[11]. Likewise, this gelatinase might also degrade different matrix substrates including collagen type I, V, VII, X and XI, elastin, fibronectin and laminin. In addition to these extracellular membrane components, MMP-9 cleaves different bioactive molecules, such as growth factors, cytokines, chemokines and also pro-MMPs (pro-MMP-2, pro-MMP-9 and pro-MMP13) and contributes to transform these molecules into their active forms^[12]. Various leukocyte subsets (including neutrophils, monocytes/macrophages and T lymphocytes) produce and release MMP-9.

Although MMP-9 is virtually absent in native livers, it is highly expressed in damaged livers after I/R injury^[13]. Its role has been investigated by Hamada and coworkers^[14], using MMP-9 deficient mice and mice treated with a specific neutralizing anti-MMP9 antibody. The authors demonstrated that, when MMP-9 is inhibited, mice were characterized by significant improvement in liver preservation outcomes. This beneficial effect (in both MMP-9 knockout and neutralizing antibody-treated mice) was also associated with a reduction of leukocyte recruitment and cytokine expression within this organ^[14]. Finally, in a next important step, Nicoud and coworkers demonstrated a direct relationship between the hepatic I/R-induced elevations in MMP-9 and the growth of metastatic colorectal carcinoma^[15]. To achieve this goal, they have subjected mice to hepatic ischemia after tumor cell injection and treated them with or without doxycycline (a broad-spectrum MMP inhibitor). Mice subjected to 30 min of 70% liver ischemia at the time of the tumor inoculation developed significantly larger tumor (expressed as number and volume), and, concomitantly, they were characterized by elevated MMP-9 levels in the systemic circulation and within liver. Accordingly, treatment with the MMP inhibitor strongly reduced the number and volume of the colorectal carcinoma metastasis in the liver. These results indicate that the inhibition of MMP-9 after the hepatic surgical resection of colorectal carcinoma metastases might be clinically relevant to prevent tumor relapse.

CONCLUSION

In summary, these studies have provided important and novel insights on the pivotal role of MMP-9 in the hepatic growth of colorectal carcinoma metastases. Furthermore, a therapeutic strategy targeting the early inhibition of MMP-9 might be a very promising approach to reduce the hepatic metastasis relapse following surgical manipulation of the liver. These preliminary results from basic research also represent a relevant input for developing more selective pharmacological inhibitors of MMP-9 to be tested *in vivo* in animal models of hepatic cancer dissemination. Although clinical studies investigating the role of MMP-9 in human beings are still lacking, these animal studies might suggest the scientific rationale for future applications targeting MMP-9 activity and expression in cancer care and prevention.

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