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Data mining and manual curation of published microarray datasets to establish a multi-gene panel for prediction of liver metastasis

Kanisha Shah [a], Shanaya Patel [a], Sheefa Mirza [b], Apexa Raval [a], Rakesh M Rawal [a,*]

[a] Division of Medicinal Chemistry and Pharmacogenomics, Department of Cancer Biology, The Gujarat Cancer and Research Institute, Ahmedabad, Gujarat, India
[b] Department of Life Science, Gujarat University, Ahmedabad, Gujarat, India

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ABSTRACT

Liver metastasis is associated with frequent occurrence and poor prognosis in patients with more common neoplastic diseases such as colorectal, breast, pancreas and lung. The poor 5-year survival rate can be attributed to factors such as aggressiveness of the disease, late diagnosis, resistance to therapy and low therapeutic response. These failures are associated with the complexity of the multifaceted metastatic process and the molecular mechanism underlying this cascade still remains unclear. Moreover, this complex cascade is driven by the acquisition of genetic and/or epigenetic alterations within tumor cells and also the co-option of non-neoplastic stromal cells, which together provide early metastatic cells, the traits needed to generate macroscopic metastases. Therefore, considering the heterogeneity of various mutations in tumorigenesis and understanding the nature of genes involved in the metastatic disease has become an utmost priority. In spite of numerous efforts being made to elucidate molecular and cellular mechanisms underlying tumorigenesis, cancer metastases still poses a threat to the modern world. Specific markers have been investigated in the hope of developing a deeper understanding of their role in liver metastases and developing newer therapeutic strategies. Thus, this review encompasses the functional relevance of almost all the biomarkers established to date with a special emphasis on a common 13-gene signature pattern specific for liver metastasis and their potential role in early prediction of metastatic event for improving the diagnosis, prognosis and treatment of patients with hepatic metastasis

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* Corresponding author at: Dept. of Cancer Biology, The Gujarat Cancer and Research Institute, NCH Campus, Asarwa, Ahmedabad-380016, Gujarat, India.
E-mail address: rakeshmrawal@gmail.com (R.M. Rawal).

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1. Introduction

Metastasis, a sequential cascade of events characterized by dissociation, invasion, intravasation, extravasation, and dormancy is regulated by a number of signalling pathways (Fidler, 2003; Talmadge and Fidler, 2010) and accounts for 90% of all cancer related deaths globally. Inspite of the recent advancements in current therapeutic modalities, prevention of metastatic cell dissemination and secondary tumor formation still remains a major challenging issue. The relative 5 year survival rate remains disappointingly low for the past few decades which can be attributed to poor prognosis in advanced stages of solid tumors, low response rate to current therapy, aggressiveness, high risk of recurrence and relapse at the primary site of the disease (Bozic et al., 2010; Chaffer and Weinberg, 2011; Leber and Efferth, 2009; Nguyen et al., 2009; Schmidt-Kittler et al., 2003).

The biological heterogeneity of the cancerous cells in the primary as well as secondary tumors is one of the major reasons accountable for the failure in treatment of metastases (Bosch et al., 2004, Talmadge and Fidler, 2010). Once the cells arrive at the secondary organ sites, they have several fates and it is the interaction with the organ microenvironment that determines whether the cancer cells will progress towards metastasis or they will remain dormant and/or completely disappear. The most common secondary sites where the tumor cells metastasize are lymph nodes, brain, bone, liver and lung. The other secondary metastatic sites include adrenal gland, spleen, kidney, ovary and thyroid (Alexander et al., 2001). In spite of this a lot of questions remain still unanswered - What attracts tumor cells to organ specific metastatic microenvironment? What sustains the continued existence of disseminated tumor cells in a specific organ site? What induces the tumor cells to proliferate? Are the survival and growth factors for metastases in a certain metastatic microenvironment similar or different from survival and growth factors for metastases from the same primary tumor in a different metastatic microenvironment? (Bosch et al., 2004).

Thus, there is a dire need to understand the pathogenesis of organ specific metastasis on cellular and molecular levels and also to assess and target new molecular biomarkers having a vital role in progression, invasion and migration of carcinogenesis.

1.1. Liver metastasis

Metastatic hepatic tumors, one of the most significant targets for organ-specific metastasis in various cancer types such as pancreatic, breast, lung and stomach, are more prevalent as compared to primary liver tumors and is predominantly the sole site of metastasis for colorectal cancer (CRC) (Alexander et al., 2001; Nguyen et al., 2009). The high incidence of liver metastases has been attributed to two mechanisms (1) the rate of metastatic deposits increase in the liver due to the dual blood supply from the portal and the systemic circulation and (2) the hepatic sinusoidal epithelium arrangements that allows easier penetration of metastatic cells into the hepatic parenchyma (Bosch et al., 2004; Feldman et al., 2002). In majority patients, the presence of liver metastasis is asymptomatic but in patients with symptomatic liver metastases ascites, hepatomegaly, abdominal fullness, hepatic pain, jaundice, anorexia, malaise, fatigue, weight loss and/or fever are the most common features of the disease.

Despite compelling improvements in surgical techniques, general patient care, local and systemic treatment options, detection and management of metastatic liver tumors is still unsettled and the poor prognosis of the disease only underlines the need to diagnose and treat the malignant lesion earlier. A significant feature of metastasis is the ability of different tumors to colonize the same or different organ sites. These findings have prompted a quest to identify the genes that support metastasis to particular organs; however it still remains unclear as to what extent these genes are used by various tumor types that metastasize to the same organ (Nguyen et al., 2009). Recent advancements have identified a limited number of organ specific genes that aid complementary and occasionally redundant functions responsible for the specific changes in the metastatic cascade that together determine the aggressiveness of the disease (Budczies et al., 2015; Fisher and Fisher, 1963; Valastyan and Weinberg, 2011). These signatures comprise of transcription factors/chromatin modifiers and microRNAs which largely regulate the genes involved in cancer metastasis (Nguyen and Massagué, 2007). Furthermore, contradictory facts strongly suggest that it is a limited number of signalling pathways rather than a group of independent regulators that may have a plausible role in controlling the metastatic gene signature (Lalor et al., 2006).

These evidences prompted us to explore datasets of various liver metastasis microarray studies with primary tumors at multiple sites which eventually led to the identification of a common 13 gene signature pattern irrespective of the various discrepancies. Thus, this review aims to discuss the functional relevance of these putative genes in liver metastasis with a hope to elucidate their underlying mechanism and highlight their potential role as probable diagnostic, prognostic or therapeutic biomarkers. This review further highlights the undisputable contribution of this genetic signature in regulating the aggressiveness and invasiveness of the disease.

2. Materials and methods

2.1. Search strategy

An electronic database search was performed using the MEDLINE/PubMed, EMBASE and ENDNOTE resources to retrieve various relevant articles related to Microarray studies involving liver metastasis of the past decade (1st January 2005 to 31st December 2015). Search headings such as “Microarray experiments”, “Microarray studies” combined with the Boolean operator ‘AND’ were used while terms like “colorectal liver metastases”, “colorectal hepatic metastases”, “pancreatic liver metastases”, “pancreatic hepatic metastases”, “breast liver metastases”, “breast hepatic metastases” were used as subheadings.

2.2. Study review and eligibility criteria

Various databases were explored to identify microarray studies that compared the expression of primary tumors of various origins (colorectal, pancreas, breast) against distant liver metastases. The pre-requisite inclusion criteria for the study comprised of, (1) only human tumors, (2) expression analysis of primary tumor versus distant metastatic tumors, (3) microarray studies conducted using platforms Affy U133A, Hs Operon V2 and Incyte UniGEM2. The exclusion criteria required