Surgical Oncology 26 (2017) 219–228

Contents lists available at ScienceDirect

Surgical Oncology

journal homepage: www.elsevier.com/locate/suronc

Role of exosomes in treatment of hepatocellular carcinoma

Demetrios Moris, MD, MSc, PhD, MACS [a], Eliza W. Beal, MD [a], Jeffery Chakedis, MD [a], Richard A. Burkhart, MD [b], Carl Schmidt, MD [a], Mary Dillhoff, MD [a], Xufeng Zhang, MD [a], Stamatios Theocharis, MD, PhD [c], Timothy M. Pawlik, MD, MPH, PhD, FACS, FRACS (Hon.) Professor and Chair [a, *]

[a] Department of Surgery, Division of Surgical Oncology, The Ohio State University Wexner Medical Center and James Cancer Hospital and Solove Research Institute, Columbus, OH, USA
[b] Department of Surgery, Division of Hepatobiliary and Pancreatic Surgery, Johns Hopkins Hospital, Baltimore, MD, USA
[c] First Department of Pathology, Medical School, National and Kapodistrian University of Athens, Athens, Greece

ARTICLE INFO

Article history:
Received 29 March 2017
Accepted 24 April 2017

Keywords:
Exosomes
Liver
Biomarkers
Hepatocellular carcinoma
miRNA
Therapy
Hepatitis
Cirrhosis

ABSTRACT

Exosomes are nanovesicles that may play a role in intercellular communication by acting as carriers of functional contents such as proteins, lipids, RNA molecules and circulating DNA from donor to recipient cells. In addition, exosomes may play a potential role in immunosurveillance and tumor pathogenesis and progression. Recently, research has increasingly focused on the role of exosomes in hepatocellular carcinoma (HCC), the most common primary liver malignancy. We herein review data on emerging experimental and clinical studies focused on the role of exosomes in the pathogenesis, diagnosis, progression and chemotherapy response of patients with HCC. Beyond their diagnostic value in HCC, exosomes are involved in different mechanisms of HCC tumor pathogenesis and progression including angiogenesis and immune escape. Moreover, exosomes have been demonstrated to change the tumor microenvironment to a less tolerogenic state, favoring immune response and tumor suppression. These results underline a practical and potentially feasible role of exosomes in the treatment of patients with HCC, both as a target and a vehicle for drug design. Future studies will need to further elucidate the exact role and reliability of exosomes as screening, diagnostic and treatment targets in patients with HCC.

Contents

1. Introduction 220
2. Exosome biology and role in cancer 220
3. Exosome involvement in liver tumor oncogenesis 221
   3.1. Exosomal derived nucleic acids as a mechanism of action 221
   3.2. Exosomes and HCC angiogenesis 222
   3.3. Mesenchymal stem cell-derived exosomes inhibit HCC development 223
   3.4. Exosomes and HCC response to chemotherapy 223
   3.5. Exosomes and immune processes in HCC 223
   3.6. Exosomes and HCC in the setting of chronic liver disease 224
   3.7. Exosomes and HCC in liver transplant (LT) patients 225
4. Obstacles and future perspectives 225
5. Conclusions 225

* Corresponding author. Department of Surgery, The Urban Meyer III and Shelley Meyer Chair for Cancer Research, Professor of Surgery, Oncology, Health Services Management and Policy, The Ohio State University, Wexner Medical Center, 395 W. 12th Ave., Suite 670, USA.
E-mail address: tim.pawlik@osumc.edu (T.M. Pawlik).

http://dx.doi.org/10.1016/j.suronc.2017.04.005
0960-7404/

Funding 225
Conflict of interest 225
References 225

1. Introduction

Primary liver cancers, including hepatocellular carcinoma (HCC) and is the second leading cause of cancer-related death worldwide and is increasing in incidence. In 2013 there were an estimated 30,640 new liver cancers diagnosed in the United States and 21,670 deaths [1]. The incidences of HCC varies among different age groups, genders, races and geographic region, likely due to a variable distribution of major etiologic factors [2]. Despite improved prevention and screening efforts, as well as the development of new technologies for diagnosis and treatment, the incidence of HCC has doubled, and mortality rates have increased [2,3]. The primary risk factor for HCC, which is present in up to 70–90% of patients, is chronic hepatic inflammation progressing and/or cirrhosis [4,5]. The majority of HCC cases worldwide are related to chronic viral hepatitis and hepatitis B virus (HBV) infection [6]. Other common risk factors include hepatitis C virus (HCV) infection, alcohol-induced liver disease (ALD), and nonalcoholic steatohepatitis (NASH) [6,7]. Current curative treatments include liver transplantation or surgical resection. Surgical resection is generally associated with long-term survival of 50%–70%, whereas 5 years overall survival among patients with early-stage disease who undergo transplantation is about 75%–85%. Unfortunately, less than 30% of patients with HCC are candidates for surgical management due to advanced disease at the time of presentation [6,8,9].

The goal of any surveillance program is to increase early detection thereby allowing for an increased chance at curative surgical intervention. In general, surveillance diagnostics typically include serum biomarkers such as alpha-fetoprotein (AFP), radiological imaging using abdominal ultrasound (US), computed tomography (CT), and magnetic resonance (MRI), and liver biopsy [10]. Serum AFP levels are elevated in 30% of patients with HCC and AFP levels > 400 ng/ml are highly correlated with the presence of HCC [10]. However, AFP lacks the sensitivity necessary for accurate diagnosis and often misses small early-stage tumors. As such, there is a need for more effective biomarkers to improve detection of small tumors.

Extracellular vesicles are one family of potential biomarkers for malignancy. Extracellular vesicles are packets of cellular proteins, lipids, DNA and RNA released by cells into the extracellular space and enveloped by a portion of the cellular membrane. Mounting evidence indicates that these vesicles can also transfer their content to other cells as a mechanism of intercellular communication [11,12]. Exosomes, one subtype of extracellular vesicle, have been implicated in many normal biologic and pathologic processes including cancer progression, metastasis, immune modulation, angiogenesis, and tissue regeneration. Exosomes have also been identified as potential tools in cancer diagnosis and treatment [13–19]. The ability to selectively manipulate exosome content, through either an exogenous or endogenous approaches, may offer further opportunities for unique therapies. The aim of the current review is to summarize and critically evaluate the role of exosomes in the natural history and treatment of patients with HCC.

2. Exosome biology and role in cancer

Exosomes are multiform, spherical to cup-shaped, nanovesicles of 40–100 nm diameter that are secreted by many cell types (Fig. 1). Exosomes can be found in most body fluids, including urine and blood, as well as in supernatants of cultured cells [20]. Exosomes are produced during the activation of the recycling endosomal pathway, which involves formation of endosomes and multivesicular bodies (MVB), and are secreted with the help of the Rab family of GTPases (Rab 27a, b) [21]. Exosomes have variable contents and have been found to enclose lipids, and multiple types of proteins including membrane fusion-related proteins, proteins involved in vesicle formation, integral membrane proteins, components of the major histocompatibility complex (MHC) classes I and II, proteins related to the cytoskeleton and cell metabolism and cell surface proteins involved in oncogenesis such as MET and mutant KRAS [22–24]. Additionally, nucleic acid cargo including mRNA, miRNA (miR), long non-coding RNAs (lncRNAs) and DNA have also been detected [25,26]. The cellular membrane that envelops exosomes helps to protect the cargo from enzymatic degradation [27]. After delivery, exosomal cargo can regulate gene expression via de novo translation and post-translation regulation of target mRNAs [28,29].

Exosomes have multiple roles in the tumor microenvironment and exosome-mediated communication is thought to be crucial for cancer cell survival. Exosomes may be involved in tumor initiation, growth, progression and chemotherapy resistance through activation of stromal fibroblasts, interaction with the extracellular matrix, generation of the pre-metastatic niche, suppression of the host immune response, and induction of angiogenesis [25,30–34]. The creation of an immunosuppressive microenvironment is an important component of tumor pathogenesis and exosomes have been implicated in many immunosuppressive processes [33–35].

Cancer cells secrete more exosomes than non-transformed cells and exosome-mediated intracellular communication appears to play a role in the cellular adaptation to cancer-associated stress through autocrine, paracrine, and endocrine mechanisms [36,37]. Adaptation of tumor cells to stressors such as hypoxia, starvation or chemotherapeutic agents underlie the biology of cancer progression [37]. Exosomal secretion from cancer cells is induced through a p53 based mechanism and increased translation of the tumor suppressor-activated pathway 6 (TSAP6) genes [38]. RISC-loading complex proteins, DICER, TRBP and AGO2, which are involved in miR biosynthesis and promote tumorigenesis, have been noted in cancer-derived exosomes [39]. Transforming growth factor-β (TGF-β), derived from exosomes, can induce differentiation of fibroblasts into tumor-supporting myofibroblasts. Furthermore, exosomes from malignant cells are able to convert adipose-derived mesenchymal stem cells (MSC) into myofibroblast-like cells, which in turn support tumor growth and angiogenesis [40]. The transfer of miR via exosomes is emerging as a novel mechanism of regulating cellular function, including cell metabolism, in several malignancies [41–44].

Angiogenesis may also be stimulated by exosomes released under hypoxic conditions [45]. Recently miR-126 was reported to regulate angiogenesis and cancer metabolism through the insulin receptor substrate-1 (IRS1), an adaptor protein with a role in metabolism, growth-promotion and malignant transformation [46]. Alterations in IRS1 expression have been documented for certain neoplastic diseases [46–50]. The mechanism by which IRS1