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Altered gene products involved in the malignant reprogramming of cancer stem/progenitor cells and multitargeted therapies

Murielle Mimeault *, Surinder K. Batra *

Department of Biochemistry and Molecular Biology, College of Medicine, Fred & Pamela Buffett Cancer Center, Eppley Cancer Institute, University of Nebraska Medical Center, Omaha, NE 68198-5870, USA

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ABSTRACT

Recent studies in the field of cancer stem cells have revealed that the alterations in key gene products involved in the epithelial–mesenchymal transition (EMT) program, altered metabolic pathways such as enhanced glycolysis, lipogenesis and/or autophagy and treatment resistance may occur in cancer stem/progenitor cells and their progenies during cancer progression. Particularly, the sustained activation of diverse developmental cascades such as hedgehog, epidermal growth factor receptor (EGFR), Wnt/β-catenin, Notch, transforming growth factor-β (TGF-β)/TGF-βR receptors and/or stromal cell-derived factor-1 (SDF-1)/CXC chemokine receptor 4 (CXCR4) can play critical functions for high self-renewal potential, survival, invasion and metastases of cancer stem/progenitor cells and their progenies. It has also been observed that cancer cells may be reprogrammed to re-express different pluripotency-associated stem cell-like markers such as Myc, Oct-3/4, Nanog and Sox-2 along the EMT process and under stressful and hypoxic conditions. Moreover, the enhanced expression and/or activities of some drug resistance-associated molecules such as Bcl-2, Akt/molecular target of rapamycin (mTOR), nuclear factor-kappaB (NF-κB), hypoxia-inducible factors (HIFs), macrophage inhibitory cytokine-1 (MIC-1) and ATP-binding cassette (ABC) multidrug transporters frequently occur in cancer cells during cancer

Abbreviations: ABC, ATP-binding cassette; ABCG2/BCRP, breast cancer related protein; ACC, acetyl-CoA carboxylase; ALDH, aldehyde dehydrogenase; AMPK, AMP-activated protein kinase; BMI-1, B lymphoma Mo-MLV insertion region 1 homolog; CAIX, carbonic anhydrase IX; COX-2, cyclooxygenase-2; CPA, cyclophosphamide; CXCR4, CXC chemokine receptor 4; DEAB, diethylaminobenzaldehyde; DETC, diethyldithiocarbamate; DRAM1, DNA-damage regulated autophagy modulator protein 1; ECM, extracellular matrix; EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition; ESA, epithelial-specific antigen; F-6-P, fructose-6-phosphate; F-1,6-P, fructose-1,6-phosphate; FASN, fatty acid synthase; Fzd, Frizzled receptor; G-6-p, glucose-6-phosphate; GAPDH, glyceraldehyde 3-phosphate dehydrogenase; GBM, glioblastoma multiforme; GLUTs, glucose transporters; GPI, glucose-6-phosphate isomerase; HA, hyaluronan; HGF, hepatocyte growth factor; HIFs, hypoxia-inducible factors; HK, hexokinase; HMG-CoA reductase, 3-hydroxy-3-methyl-glutaryl-CoA reductase; Hsp, heat shock protein; IGF-1R, insulin-like growth factor 1-receptor; IL, interleukin; KIT, stem cell factor receptor; LDH, lactate dehydrogenase; MAPKs, mitogen-activated protein kinases; MET, hepatocyte growth factor/scatter factor receptor; MIC-1, macrophage inhibitory cytokine-1; MMPs, matrix metalloproteases; Myc, V-myc myelocytomatosis viral oncogene homolog (avian); mTOR, molecular target of rapamycin; NSCLC, non-small cell lung cancer; NF-κB, nuclear factor-kappaB; NOD-SCID, non-obese diabetic-severe combined immunodeficient; Oct-3/4, octamer-binding transcription factor-3/4; PDGF, platelet-derived growth factor; PDGFRs, platelet-derived growth factor receptors; PDTC, pyrrolidinethiocarbamate; PEP, phosphoenolpyruvic acid; PFK, phosphofructokinase; 2-PG, glycerate 2-phosphate; 3-PG, glycerate 3-phosphate; P-gp, P-glycoprotein; PGM, phosphoglyceromutase; PI3K, phosphatidylinositol 3'-kinase; PK, pyruvate kinase; PTCH, pathched receptor; PTEN, phosphatase and tensin homolog deleted on chromosome 10; ROS, reactive oxygen species; SCC, squamous cell carcinoma; SCF, stem cell factor; SDF-1, stromal cell-derived factor-1; SHH, sonic hedgehog ligand; shRNA, small hairpin RNA; siRNA, small interfering RNA; SMO, smoothened; SP, side population; SREBPs, transcription factor sterol regulatory element-binding proteins; SRY or SOX-2, sex determining region Y-box 2; TG2, tissue transglutaminase; TGF-β, transforming growth factor-β; TGF-βR, transforming growth factor-beta receptor; TRAIL, apoptotic tumor necrosis factor-related apoptosis-inducing ligand; uPA, urokinase plasminogen activator; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor and Wnt, Wingless ligand.

* Corresponding authors. Tel.: +1 402559 5455; fax: +1 402 559 6650.
E-mail addresses: mmimeault@unmc.edu (M. Mimeault), sbatra@unmc.edu (S.K. Batra).

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progression and metastases. These molecular events may cooperate for the survival and acquisition of a more aggressive and migratory behavior by cancer stem/progenitor cells and their progenies during cancer transition to metastatic and recurrent disease states. Of therapeutic interest, these altered gene products may also be exploited as molecular biomarkers and therapeutic targets to develop novel multitargeted strategies for improving current cancer therapies and preventing disease relapse.

1. Introduction

Recent advances in cancer research have led to the identification of distinct gene products that are often deregulated in cancer cells during primary cancer progression and metastases at surrounding and distant tissues and associated with a poor prognosis of cancer patients (Bismar et al., 2006; Glinsky et al., 2005; Manjili et al., 2012; Marchini et al., 2010; Markert et al., 2011; Perez-Villamil et al., 2012; Sergeant et al., 2012; Van Laar, 2012; Varambally et al., 2005). Although this important advance, the heterogeneity of the most cancers and progressive changes of the expression and/or activity of numerous candidate biomarkers and therapeutic targets during disease progression and between patients have limited their applications in clinical settings. It is become evident that the validation of novel gene signatures combining different biomarkers and/or molecular targets in cancer cells and their local microenvironment will be necessary for overcoming the intervariability between cancer subtypes and improving the therapeutic management and survival of cancer patients.

Importantly, a growing body of experimental evidence has revealed that cancer stem/progenitor cells endowed with stem cell-like properties, also designated as cancer-, tumor- and metastasis-initiating cells, can play critical functions for the leukemia development or tumor growth, metastases, treatment resistance and disease relapse. It has been shown that the most cancers may originate from the malignant transformation of immature tissue-resident adult stem/progenitor cells or their early progenies endowed with a high self-renewal ability and aberrant differentiation potential (Mimeault and Batra, 2010b,c,d, 2013). In support with this, cancer stem/progenitor cells expressing specific stem cell-like markers such as CD133, CD44^{high}, aldehyde dehydrogenase (ALDH^{high}), CD90, CXC chemokine receptor 4 (CXCR4^{high}) and high levels of ATP-binding cassette (ABC) multidrug transporters have been identified and isolated from primary and metastatic tissues of cancer patients and established cancer cell lines (Al-Hajj et al., 2003; Bapat et al., 2005; Chiba et al., 2006, 2007, 2008; Eramo et al., 2008; Fillmore and Kuperwasser, 2008; Friel et al., 2008; Galli et al., 2004; Hemmati et al., 2003, 2007; Huang et al., 2009; Kim et al., 2005; Ma et al., 2007, 2008a,b; Maitland et al., 2006; Marsden et al., 2012; Mimeault et al., 2007b, 2012; Mimeault and Batra, 2011; Mimeault and Batra, 2013; Mitsutake et al., 2007; Ponti et al., 2005; Prince et al., 2007; Qin et al., 2012; Ricci-Vitiani et al., 2007; She et al., 2008; Shi et al., 2008; Singh et al., 2004; Sung et al., 2008; Wright et al., 2008; Yang et al., 2008; Yu et al., 2008; Yuan et al., 2004; Zhang et al., 2012a). The cancer types harboring a cancer stem/progenitor cell subpopulation with stem cell-like properties include leukemias, lymphomas, sarcomas, melanomas, brain tumors and diverse epithelial cancers such as skin, head and neck, cervical, lung, liver, thyroid, renal, esophageal, gastrointestinal, colon, bladder, pancreatic, prostate, ovarian and breast cancers (Al-Hajj et al., 2003; Bapat et al., 2005; Chiba et al., 2008; Eramo et al., 2008; Fillmore and Kuperwasser, 2008; Frank et al., 2005; Friel et al., 2008; Galli et al., 2004; Hemmati et al., 2003; Hermann et al., 2007; Huang et al., 2009; Kim et al., 2005; Maitland et al., 2006; Marsden et al., 2012; Ponti et al., 2005; Prince et al., 2007; Qin et al., 2012; Ricci-Vitiani et al., 2007; She et al., 2008; Shi et al., 2008; Singh et al., 2004; Sung et al., 2008; Wright et al., 2008; Yang et al., 2008; Yu et al., 2008; Yuan et al., 2004; Zhang et al., 2008a). It has been observed that cancer stem/progenitor cells displayed higher clonogenic and sphere-forming abilities than their differentiated progenies *in vitro* and were able to give rise to the total cancer cell mass that reconstituted the histological architecture and molecular characteristics closely resembling to original patient's cancer subtypes *in vivo* (Al-Hajj et al., 2003; Bapat et al., 2005; Chiba et al., 2008; Eramo et al., 2008; Fillmore and Kuperwasser, 2008; Frank et al., 2005; Friel et al., 2008; Galli et al., 2004; Hemmati et al., 2003; Hermann et al., 2007; Huang et al., 2009; Kim et al., 2005; Maitland et al., 2006; Marsden et al., 2012; Ponti et al., 2005; Prince et al., 2007; Qin et al., 2012; Ricci-Vitiani et al., 2007; She et al., 2008; Shi et al., 2008; Singh et al., 2004; Sung et al., 2008; Wright et al., 2008; Yang et al., 2008; Yu et al., 2008; Yuan et al., 2004; Zhang et al., 2008a). It has also been noted that different cancer subtypes may contain distinct subsets and/or a different number of cancer stem/progenitor cells during primary cancer progression and metastasis formation at distant sites as well as before or after therapy initiation and disease recurrence (Bao et al., 2006; Das et al., 2008; Dylla et al., 2008; Griffero et al., 2009; Huang et al., 2009; Kelly et al., 2007; Liu et al., 2006a; Mimeault and Batra, 2013; Quintana et al., 2008; Schmidt, 2008; Shmelkov et al., 2008).

In addition, accumulating lines of evidence have also indicated that cancer- and metastasis-initiating cells with stem cell-like features may express some drug resistance-associated molecules and be more resistant than their differentiated progenies to current anti-hormonal, radiation and chemotherapeutic treatments (Alvero et al., 2009; Bao et al., 2006; Chiba et al., 2008; Fillmore and Kuperwasser, 2008; Frank et al., 2005; Friel et al., 2008; Hamada et al., 2012; Haraguchi et al., 2006; Hermann et al., 2007; Hirschmann-Jax et al., 2004; Huang et al., 2009; Kurrey et al., 2009; Lee et al., 2012; Liu et al., 2006a;