Biochimica et Biophysica Acta 1855 (2015) 43–49

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Epithelial–mesenchymal transition in pancreatic cancer: Is it a clinically significant factor?

Jia-Hao Jiang [a,b,c,1], Chen Liu [a,c,1], He Cheng [a,b,c,1], Yu Lu [a,c], Yi Qin [a,c], Yong-Feng Xu [a,b,c], Jin Xu [a,b,c], Jiang Long [a,b,c], Liang Liu [a,b,c], Quan-Xing Ni [a,b,c], Xian-Jun Yu [a,b,c,*]

[a] Department of Pancreatic and Hepatobiliary Surgery, Fudan University Shanghai Cancer Center, Shanghai 200032, PR China
[b] Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, PR China
[c] Pancreatic Cancer Institute, Fudan University, Shanghai 200032, PR China

ARTICLE INFO

Article history:
Received 1 January 2014
Received in revised form 31 October 2014
Accepted 17 November 2014
Available online 26 November 2014

Keywords:
Epithelial–mesenchymal transition
Pancreatic cancer
Tumorigenesis
Metastasis
Prognosis
Therapy

ABSTRACT

Pancreatic cancer is one of the most aggressive solid malignancies. This aggressiveness is partly attributable to extensive local tumor invasion and early systemic dissemination as well as resistance to chemotherapy. Epithelial–mesenchymal transition (EMT) plays fundamental roles in embryonic development and in the differentiation of normal tissues and organs. EMT also plays critical roles in tumor formation, dissemination and drug resistance in pancreatic cancer. Emerging data suggest that inhibiting EMT may reverse the EMT phenotype and enhance the efficacy of chemotherapeutic agents against pancreatic cancer cells. Thus, an understanding of the molecular biology of EMT in pancreatic cancer may provide insights into the mechanisms of tumor invasion and metastatic progression and facilitate the development of alternative therapeutic approaches to improve the treatment outcomes for patients suffering from pancreatic cancer.

Contents

Abbreviations: EMT, epithelial–mesenchymal transition; CSC, cancer stem cell; PSC, pancreatic stellate cell; TGF-β, transforming growth factor β; ZEB, zinc-finger E-box binding homeobox; HDAC, histone deacetylase; PDGF, platelet-derived growth factor; EGF, epidermal growth factor; HGF, hepatocyte growth factor; TNF-α, tumor necrosis factor α; IL, interleukin; COX-2, cyclooxygenase-2

* Corresponding author at: No. 270, Dong'An Road, Xuhui District, Shanghai 200032, PR China. Tel.: +86 21 64175590 1306; fax: +86 21 64031446.
E-mail address: yuxianjun88@hotmail.com (X.-J. Yu).
[1] These authors contributed equally to this article.

http://dx.doi.org/10.1016/j.bbcan.2014.11.004
0304-419X/

1. Introduction

Pancreatic cancer is the eighth most common cause of cancer-related deaths worldwide and has an extremely poor prognosis, with an overall 5-year survival rate of <5% [1]. The causes of pancreatic cancer are unclear. Many risk factors have been associated with an increased incidence of pancreatic cancer, including smoking, alcohol intake, diabetes, chronic pancreatitis, diet, obesity and family history [2]. Although notable improvements in survival have been achieved for many cancers in recent decades, pancreatic cancer survival has improved very little [3,4]. Pancreatic cancer is typically diagnosed at an advanced stage, with more than 80% of pancreatic cancer patients presenting with locoregional spread and/or distant metastasis; this delayed diagnosis is a major obstacle to long-term survival [5]. Therefore, an understanding of the molecular biology underlying the invasion and metastasis of pancreatic cancer is required to improve the rate of survival.

Epithelial–mesenchymal transition (EMT) plays fundamental roles in embryonic development and in the differentiation of multiple tissues and organs as well as in the metastasis of cancer cells [6]. Upon undergoing EMT, cells are endowed with migratory and invasive properties that allow them to migrate to distant organs through the extracellular matrix, enabling cell differentiation into multiple types during development and the metastatic initiation of cancer cells [7]. EMT is characterized by a loss of cell–cell contacts through the inhibition of epithelial markers, such as E-cadherin expression, and the acquisition of mesenchymal features, such as the up-regulation of the mesenchymal markers N-cadherin, vimentin, Twist, Snail1 and Snail2 [8].

Numerous data have indicated that EMT occurs in the development and progression of human solid tumors, including pancreatic cancer. This review presents the events in pancreatic cancer tumorigenesis, progression and prognosis. Finally, we discuss the impact of EMT on therapeutic resistance and explore potential approaches to improve the clinical management of pancreatic cancer.

2. EMT and pancreatic cancer tumorigenesis

Pancreatic cancer originates from the successive acquisition of several genetic changes that enable the malignant transformation of the pancreatic ductal epithelium to intraepithelial neoplasia and, eventually, to fully invasive cancer [2]. The mutational events of pancreatic cancer include the activation of the *KRAS* oncogene and inactivation of the tumor-suppressor genes *CDKN2A*, *TP53*, *SMAD4* and *BRCA2*. *KRAS* mutations occur in more than 90% of human pancreatic cancers, representing an essential event in the initiation of the malignant transformation of normal exocrine pancreas cells [4]. Pancreatic cancer cell lines harboring *KRAS* mutations tend to exhibit EMT induction, and the EGFR/Ras pathway correlates with the genesis and promotion of EMT-induced tumor-initiating cells [9–12]. Oncogenic *KRAS* activity affects the pancreatic tumor microenvironment by regulating the infiltration of immune cells as well as specific immune cytokines and cellular signaling pathways that also play an important role in the EMT process [13]. Extensive efforts have focused on inhibiting or reversing the expression of oncogenic *KRAS*. Some progress has been achieved in mouse models, in which blocking *KRAS* activity slows pancreatic cancer growth and even induces tumor regression [13,14]. Thus, inhibiting *KRAS* directly or its effectors, such as the Akt and MAPK signaling pathways as well as the inducers of EMT, may be promising therapeutic targets for pancreatic cancer.

SMAD4 inactivation occurs in approximately 50% of pancreatic cancers, resulting in changes in the cell signaling pathway of transforming growth factor β (TGF-β). Members of the TGF-β family, which are involved in angiogenesis and regulate cell proliferation, differentiation and apoptosis, are the main and best-characterized inducers of EMT in embryonic development as well as in tumor pathogenesis [15]. The role of TGF-β in pancreatic cancer is complex. Deregulated TGF-β signaling is a common event in pancreatic cancer development and progression and is thought to promote tumor-associated pathways and the development of a tumor microenvironment [16]. TGF-β inhibitors block and even reverse the EMT process and prevent tumor metastasis *in vivo* [17]. Interestingly, *KRAS* mutations appear to be early events that occur in intraepithelial neoplasias with low- to intermediate-grade dysplasia, while *SMAD4* mutations appears to be relatively late events that occur in intraepithelial neoplasias with high-grade dysplasia and in aggressive neoplasms [4]. Mouse studies indicate that *KRAS* activation cooperates with *SMAD4* inactivation to accelerate the initiation and development of pancreatic tumors [18].

Recent studies have demonstrated that a small group of pancreatic cancer cells appear to have cancer stem cell (CSC) features, as identified by the expression of specific cell surface markers including CD44, CD24, CD133, epithelial-specific antigen (ESA), and hepatocyte growth factor (HGF), some of which may promote cell-to-cell interactions and activate many EMT-related pathways [19]. CSCs possess certain unique properties, including unlimited self-renewal, asymmetric division and differentiation into other cell types, that distinguish them from the majority of cancer cells and fuel the maintenance of tumor growth [2]. Emerging evidence suggests that EMT generates cells with stem cell properties, promotes the CSC phenotype, and therefore enhances pancreatic cancer tumorigenic and metastatic ability [19,20].

EMT programs can also be triggered by many growth factors and cellular signaling pathways, including platelet-derived growth factor (PDGF), Notch and Wnt signaling, some of which are essential for the regulation of pancreatic tumor growth (Table 1) [15,21,22]. Thus, EMT plays an important role in tumor initiation and progression in pancreatic cancer, and EMT regulators are promising candidate therapeutic targets for pancreatic cancer (Table 1) [23,24].

3. EMT and pancreatic cancer progression

3.1. E-cadherin loss and its repressors

The loss of contact inhibition of cell proliferation, a hallmark of cancer, is thought to be associated with cadherin-mediated cell–cell attachments [25]. E-cadherin is expressed in epithelial cells and plays a vital role in cell adhesion and movement. E-cadherin loss can stabilize tumor cells in the mesenchymal state, producing single migratory cells derived from epithelial tumor cells [26–28]. The loss of E-cadherin function or expression is considered a crucial step in the progression of incipient neoplasia to invasive carcinoma and a fundamental event in EMT [29]. Partial or complete loss of E-cadherin expression is particularly evident in patients with undifferentiated, noncohesive pancreatic cancers, indicating that E-cadherin loss plays an essential role in the invasive and metastatic process of pancreatic cancer cells [30–32]. E-cadherin loss can be caused by genetic or epigenetic modifications and gene promoter silencing, but the regulation of E-cadherin expression in pancreatic cancer remains unclear [33–35].

Some factors, including Snail family members, ZEB family members, bHLH family members and HDACs, are inducers of EMT as well as potent repressors of the E-cadherin promoter (Table 1) [36]. Snail-induced EMT accelerates tumor lymph node invasion and distant metastasis by repressing E-cadherin expression, enhancing the invasive ability of cancer cells and inducing immunosuppression [36–39]. Snail also alters cell proliferation and protects against cell death, which are essential for the metastatic process in tumor cells [39]. *In vivo* experiments have demonstrated that the Snail/HDAC1/HDAC2 complex promotes the pancreatic cancer metastatic process by suppressing E-cadherin expression to induce EMT in human pancreatic cancer cells, while the inhibition of HDAC *via* drug treatment restores E-cadherin expression [31]. *In vitro* studies have indicated that ZEB1 cooperates with HDAC1 and HDAC2 to bind and modify the *CDH1* promoter, while HDAC inhibition and ZEB1 knockdown cause E-cadherin expression and attenuate pancreatic cancer cell proliferation and migration [40]. These findings reveal a complex

Table 1
EMT inducers in pancreatic cancer.

EMT inducers	Function	Role in pancreatic cancer	Consequences when targeted	Refs
Molecules				
E-cadherin	Regulates cell adhesion and movement; establishes and stabilizes epithelial cell plasticity; suppresses cancer invasion	Loss of function triggers EMT, promotes metastasis and contributes to poor prognosis	Re-expression reverses EMT and inhibits cancer metastasis	[26–33]
Snail family (Snail1, Snail2 and Snail3)	Represses E-cadherin promoter; induces EMT; induces immunosuppression; alters cell proliferation and protects against cell death	Accelerates lymph node invasion and distant metastasis; induces drug resistance; contributes to poor prognosis	Inhibition of cancer metastasis; induction of immune responses	[31,36–39,64]
ZEB family (ZEB1 and ZEB2)	Represses the E-cadherin promoter; induces EMT; represses stemness-inhibiting microRNAs	Promotes tumorigenesis and cancer metastasis; maintains drug resistance; contributes to poor prognosis	Reversal of EMT; restoration of drug sensitivity	[23,28,36]
bHLH family (E47 and TWIST)	Represses E-cadherin promoter; induces EMT; regulates cell cycle, proliferation and survival	Promotes cancer metastasis	Inhibition of cell cycle progression	[15,36,37,79]
HDACs	Repress E-cadherin promoter; induce EMT; modify chromatin structure	Promote cancer metastasis; contribute to poor prognosis	Inhibition of tumor cell proliferation and migration; restoration of E-cadherin expression	[31,40,63,66]
Pathways				
Ras	Regulates cell signaling and the tumor microenvironment; drives tumor development and progression	Promotes tumor initiation and progression; contributes to poor prognosis	Slowed tumor growth; tumor regression	[13,14,22]
Notch	Regulates cell differentiation, proliferation and apoptosis; induces EMT	Promotes tumor cell migration and invasion; increases chemoresistance	Inhibition of tumor invasion and metastasis	[21]
Wnt	Regulates cell proliferation, differentiation and morphogenesis; induces EMT	Promotes tumor cell proliferation and metastasis; induces drug resistance; influences tumor–stroma interaction	Reduction of tumor cell viability; reversal of EMT; enhanced drug sensitivity	[22]
Hedgehog	Regulates embryonic development, cell regeneration and stem cell proliferation; induces EMT	Promotes stromal desmoplasia; restrains tumor progression	Acceleration of tumor growth and metastasis; increased tumor angiogenesis	[46–49]
Factors				
TGF-β	Induces EMT; regulates cell proliferation, differentiation and apoptosis	Promotes tumor invasion and metastasis; influences tumor–stroma interaction	Inhibition of EMT and prevention of tumor invasion and metastasis	[15–17]
PDGF	Regulates embryonic development, cell proliferation, cell migration and survival; induces EMT	Promotes tumor progression; influences tumor–stroma interaction	Prevention of tumor invasion and metastasis	[27,46]
HGF	Regulates cell growth and cell motility; induces EMT	Promotes tumor growth, invasion and dissemination; influences tumor–stroma interaction	Inhibition of tumor growth, migration and invasion	[19]
EGF	Regulates cell growth, proliferation and differentiation; induces EMT	Promotes tumor cell motility and invasion; influences tumor–stroma interaction; contributes to poor prognosis	Inhibition of tumor cell proliferation, invasion and metastasis	[10,46]
microRNAs	Regulate gene expression; establish epigenetic programs; affect EMT	Regulate tumor invasion and metastasis	Reversal of EMT; enhanced chemotherapeutic sensitivity	[23,24,71–74]
Stroma	Exhibits mesenchymal features; influences tumor microenvironment	Promotes tumor development and progression; induces resistance to chemotherapy and radiotherapy	Enhanced chemotherapeutic sensitivity; reinforcement of immune reaction	[42–49]
Stathmin	Regulates microtubule dynamics; induces EMT	Promotes invasion and metastasis	Stabilization of microtubules; impaired cell migration; inhibition of EMT	[56–59]

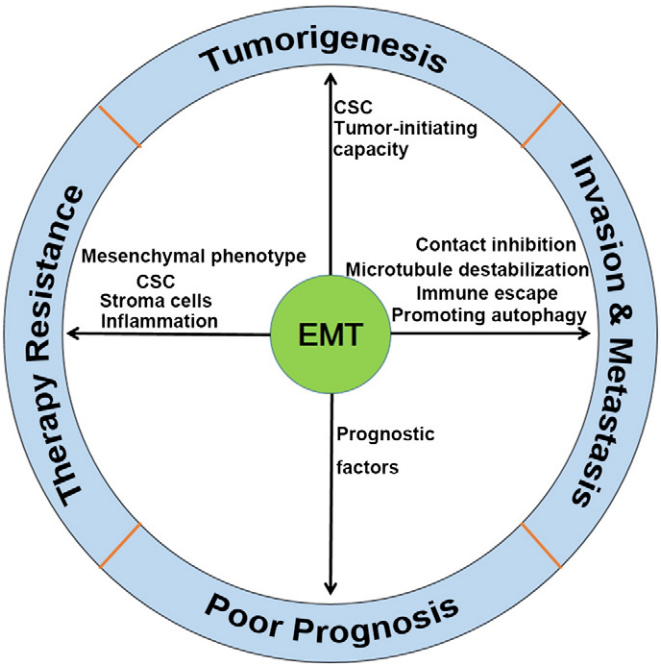

Fig. 1. The roles of EMT in pancreatic cancer. Pancreatic cancer cells with the EMT phenotype are endowed with a capacity for tumor initiation, invasion, metastasis and therapeutic resistance *via* various mechanisms; and these cells are also responsible for poor prognosis.

network of EMT regulators that connect, communicate and cooperate with each other to promote tumor development and progression (Fig. 1).

3.2. The tumor–stroma interaction

In contrast to most other solid tumors, pancreatic cancer is characterized by desmoplasia (abundant fibrotic stroma) and hypovascular aspects, which underlie the resistance of pancreatic cancer to chemotherapy [41]. The formation of a dense stroma is a histological hallmark of pancreatic cancer and constitutes a dynamic compartment that vitally affects the entire process from tumor formation and progression to metastasis [42,43]. Stroma cells exhibit mesenchymal features and EMT can cause the formation of the extensive stroma in pancreatic cancer [42,44]. The tumor–stroma interface, including communication between inflammatory elements and the immunosuppressive tumor microenvironment, plays a critical role in the process of pancreatic cancer progression [45]. Many molecules that are involved in the EMT process, including Snail, Wnt signaling, Sonic Hedgehog, TGF-β, PDGF, HGF, and EGF, can also mediate the tumor–stroma interface and induce continuous interaction between the stromal and tumor cells (Table 1) [46]. Hedgehog signaling has received substantial attention because it serves as a mediator that promotes stromal desmoplasia. Hedgehog was initially thought to promote pancreatic cancer tumorigenesis and metastasis, and Hedgehog inhibition can block pancreatic tumor invasion and metastasis [46]. However, recent studies have indicated that the stroma driven by Hedgehog signaling restrains tumor aggressive capacity and exhibits a protective role against cancer metastasis, such that Hedgehog inhibition accelerates rather than suppresses pancreatic cancer progression [47–49]. These findings have impelled researchers to change anti-cancer strategies to identify novel types of therapeutic interventions.

3.3. Inflammation

Inflammation, particularly tumor-associated inflammation, is enriched in desmoplasia and plays a vital role in promoting the initiation and progression of pancreatic cancer [50]. Inflammation stimulates the EMT process and cancer cell dissemination; accordingly, anti-inflammatory therapy with dexamethasone impedes cancer dissemination, and certain immune-related cytokines, including TGF-β, TNF-α, IL-1 and IL-6, can trigger the EMT process by regulating the expression of EMT inducers [51–53]. The inflammatory tumor microenvironment endows pancreatic cancer cells with the capacity for initiation, development and metastasis, possibly by stimulating EMT, facilitating cancer cell survival and proliferation, suppressing immunosurveillance, and inhibiting

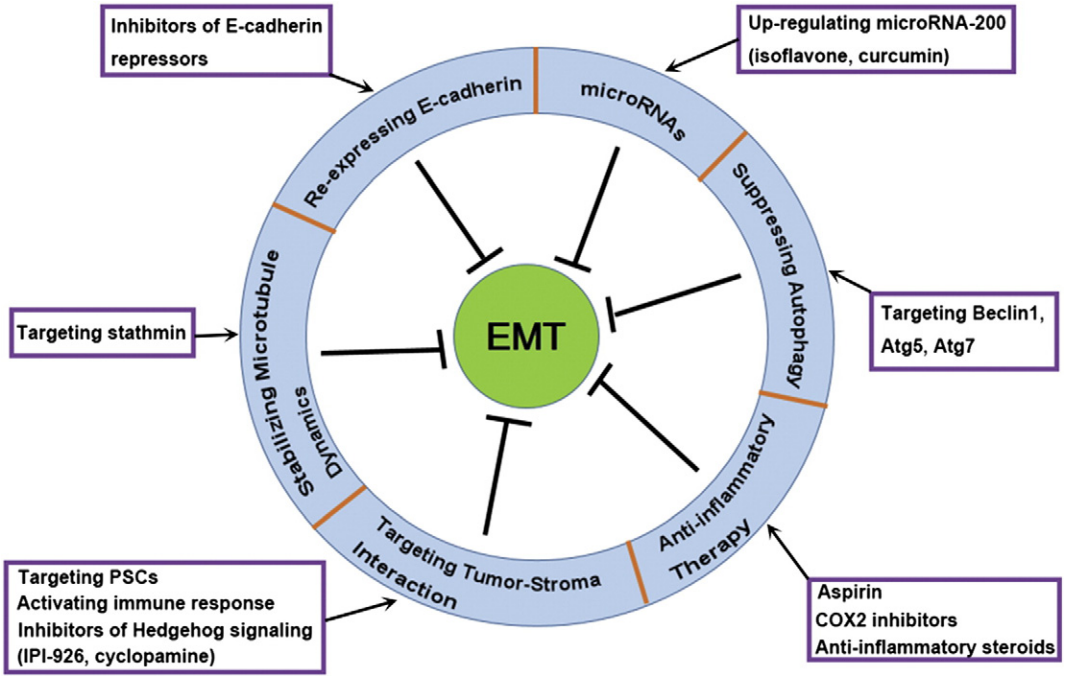

Fig. 2. Potential EMT-related therapeutic targets of pancreatic cancer. All EMT regulators can be targeted for anticancer therapy. Small-molecule inhibitors such as IPI-926 and cyclopamine, certain anti-inflammatory drugs such as aspirin, and natural agents such as isoflavone and curcumin have been developed to target the tumor microenvironment, up-regulate E-cadherin and reverse EMT. A combination of alternative approaches and conventional therapies may hold promise to improve the efficacy and utility of cancer prevention and treatment.

oncogene-induced senescence [41,54]. Thus, targeting tumor-promoting inflammation may reduce tumor incidence, slow tumor progression, and block cancer metastasis. In fact, certain anti-inflammatory drugs, such as COX2 inhibitors, aspirin, or steroids, are effective against certain human malignancies, including colon, prostate, and breast cancers and lymphoid tumors [51]. Furthermore, a combination of anti-inflammatory therapies and conventional therapies greatly improves the efficacy and utility of cancer prevention and treatment [51,55]. Therefore, as a characteristic feature of pancreatic cancer, tumor–stroma inflammation represents a new, potent therapeutic target. Interfering with the inflammatory tumor–stroma microenvironment in pancreatic cancer may stimulate immune surveillance of cancer cells, enhance the sensitivity of cancer cells to chemotherapy, and inhibit the EMT process to block cancer metastasis (Fig. 2) [52].

3.4. Microtubule dynamics

In addition to cadherin-mediated cellular morphological changes, cytoskeletal architecture and microtubule dynamics are critical factors in EMT-related cellular events. Microtubule dynamics are essential for cell migration and are regulated by stathmin, which is a notable microtubule destabilizer as well as an EMT inducer [56–58]. Stathmin overexpression is associated with more aggressive characteristics and high invasion and metastasis in various human cancers, including pancreatic cancer, and suppressing stathmin stabilizes microtubules, impairs cell migration, and inhibits EMT [57]. Thus, targeting the microtubule-destabilizing dynamics of stathmin to inhibit pancreatic cancer cell growth and dissemination represents an alternative approach to cancer therapy (Fig. 2) [59].

4. EMT and pancreatic cancer prognosis

Pancreatic cancer has a dismal prognosis due to the frequency of local invasion and early metastasis. Substantial evidence indicates that EMT status is associated with poor prognosis and adverse clinical outcomes, such as portal vein invasion and lymph node metastasis [30,60]. The mechanism of EMT affecting the prognosis of pancreatic cancer is unclear. EMT-induced cancer cell dissemination may be the main reason for poor prognosis. Moreover, cancer cells with EMT possess CSC features that represent resistance to chemotherapy and radiotherapy, which is also responsible for the frustrating therapeutic effect of pancreatic cancer (Fig. 1) [61].

The association between EMT and pancreatic cancer prognosis can be demonstrated by a large number of EMT regulators, some of which are prognostic factors for pancreatic cancer. In surgically resected pancreatic cancer tissues, EMT status is distinguished by the immunohistochemical detection of decreased E-cadherin expression and increased expression of mesenchymal markers, such as vimentin and Snail. The loss of E-cadherin expression has been correlated with adverse clinical outcomes in various types of human cancers, and is an independent predictor of poor prognosis in pancreatic cancer [62]. Some EMT regulators, such as Snail, ZEB1, and HDAC1, are overexpressed in pancreatic cancer tissues and generally correlate with E-cadherin loss and cancer metastasis, which are associated with tumor recurrence and poor long-term survival [36,40,63,64].

5. EMT and pancreatic cancer therapy

Despite recent advancements in the elucidation of the genetics and molecular biology of pancreatic cancer, survival statistics remain bleak, particularly in patients with advanced disease. Even after complete tumor removal, the clinical outcome in patients with early pancreatic cancer is unsatisfying because patients with resectable or unresectable pancreatic cancer generally have a limited response to chemotherapy [2]. EMT-phenotypic cells play a vital role in not only tumor formation, progression and metastasis but also therapeutic resistance in pancreatic cancer [65]. Tumors resistant to conventional chemotherapy exhibit a mesenchymal morphology and express certain EMT markers [65]. The tumor–stroma cell environment also affects the development of pancreatic cancer progression and therapeutic resistance [43]. Therefore, EMT regulators are abundant molecular targets for anti-cancer therapy (Fig. 2). Some progress has been made; EMT inhibition not only reverses the EMT phenotype of cancer cells but also enhances sensitivity to drug treatment in cell models and human tumors [28].

5.1. Reversing EMT

Functional loss of E-cadherin is a hallmark of EMT and can be mediated by genetic mutation, epigenetic inactivation, and transcriptional silencing of the *CHD1* gene [33]. Of these mechanisms, transcriptional silencing of *CHD1* gene expression regulated by specific transcriptional factors may be the most frequent event. These transcriptional factors act not only as intracellular inducers of EMT but also as therapeutic targets to block tumor progression (Table 1) [36]. The histone deacetylases HDAC1 and HDAC2 are regulated by Snail and ZEB1 and mediate the loss of E-cadherin expression in pancreatic cancer cells through the deacetylation of histones H3 and H4 within the *CDH1* promoter. Knockdown of Snail, ZEB1 and/or HDACs induces the reversal of EMT, the reduction of tumor cell migration and proliferation, and the enhancement of drug sensitivity [31,40]. HDAC inhibition can also suppress cell cycle progression, promote DNA repair, and induce tumor cell apoptosis and autophagy, an encouraging profile for cancer treatment. Substantial progress has been achieved in the development of HDAC inhibitors as a new anti-cancer agent, and some HDAC inhibitors have been investigated in clinical trials [66]. In addition, Snail, as a potent repressor of E-cadherin, can both increase tumor invasive ability and suppress immune responses. Snail inhibition simultaneously restrains EMT-induced cancer metastasis and immunosuppression, restoring immunocompetence in patients with malignancy [39]. These findings indicate that reversing the EMT phenotype of cancer cells may concomitantly improve other adverse outcomes generated by cancer cells, suggesting a potential oncotherapy for cancer invasion and metastasis.

5.2. Targeting the tumor–stromal interaction

Tumor stroma formation is closely related to the EMT process. Recent evidence indicates that tumor stromal cells provide a cancer-promoting microenvironment that enhances immune suppression in the tumor and the resistance of the tumor to effective treatment, including conventional chemotherapy and radiotherapy [42,46,50]. In the past decade, researchers have attempted to treat pancreatic cancer by targeting tumor–stromal interactions, including targeting pancreatic stellate cells (PSCs), inhibiting extracellular matrix deposition, suppressing angiogenesis, reversing immune suppression, and activating the immune response in pancreatic cancer [67,68]. In mouse models, drugs that deplete tumor-associated stromal tissue by inhibiting the Hedgehog signaling pathway increase intratumoral vascular density and the intratumoral concentration of gemcitabine, facilitate drug delivery and enhance the efficacy of chemotherapeutic agents against pancreatic cancers [69]. Improvements have also been achieved in the inhibition of PSC function and reinforcement of the host immune reaction [68]. These findings suggest that the microenvironment associated with the tumor–stromal interaction may be an alternative therapeutic target for pancreatic cancer.

5.3. microRNAs

MicroRNAs, the small noncoding RNA molecules that regulate gene expression, are important regulatory molecules in various biological processes, including EMT. Certain microRNAs, including microRNA-34, microRNA-141, let7, microRNA-22 and microRNA-

200, act as tumor suppressors, while other microRNAs, including microRNA-21, microRNA-155, microRNA-520, microRNA-221 and microRNA-203, exhibit oncogenic activity [70,71]. Of these microRNAs, the microRNA-200 family may be the most important in pancreatic cancer progression. Indeed, studies have highlighted the importance of microRNA-200s in regulating EMT and controlling the metastatic ability of pancreatic cancer cells [23]. The expression of the microRNA-200 family is significantly down-regulated in gemcitabine-resistant pancreatic cancer cells, which exhibit typical EMT characteristics, while re-expression of microRNA-200s reverses the EMT phenotype by up-regulating the expression of E-cadherin and down-regulating the expression of ZEB1 and ZEB2 [23,24,72]. Conversely, Snail, ZEB1 and ZEB2 also repress the expression of the microRNA-200s, forming a feedback loop of microRNAs and transcriptional repressors of E-cadherin cross-regulation to influence the EMT process and cancer metastasis [73,74]. In addition, forced expression of microRNA-200s restores the chemotherapeutic sensitivity of EMT-induced drug-resistant pancreatic tumor cells [70]. Because the aberrant expression of specific microRNAs is involved in the disease progression and drug resistance of pancreatic cancer, the inhibition or re-expression of these microRNAs may be a new strategy to block tumor progression and overcome drug resistance.

5.4. Suppressing autophagy

Autophagy, the basic physiological process that maintains cell survival by mediating the degradation of unnecessary or dysfunctional cellular components through the lysosomal pathway, accelerates cancer invasion and metastasis under conditions of starvation and hypoxia [75,76]. Recent studies have shown that autophagy promotes tumor invasion by inducing EMT and that EMT activates autophagy to maintain the resistance of tumor cells to cytotoxic T lymphocyte-mediated killing [77–79]. We have demonstrated that repressing autophagy induced by irradiation increases the radiosensitivity of pancreatic cancer cells [80]. These results indicate that autophagy, in concert with EMT, may allow tumor cells to evade immune surveillance, chemotherapy and radiotherapy, suggesting a promising therapeutic strategy in which inhibiting autophagy sensitizes resistant tumor cells with an EMT phenotype to immune therapy as well as conventional therapy [77].

6. Conclusions

The EMT process is fundamental to both physiological and pathological development. An aberrantly activated EMT phenotype is a key event in pancreatic cancer development, progression and drug resistance, and may be relevant to therapeutic approaches. Because EMT is controlled by a complex network of transcriptional regulators, cellular signaling pathways and microRNAs, small-molecule inhibitors against EMT activators will pave the way for devising targeted therapeutic approaches. The EMT process also confers cancer cells with resistance to apoptosis and senescence, immunosuppression and immunoresistance, as well as stem cell properties, which opens new avenues to develop multimodal therapies aimed at targeting tumor cells together with their microenvironment. Thus, the elucidation of the molecular biology of EMT in pancreatic cancer may provide insights into the mechanisms of tumor recurrence and metastatic progression and alternative therapeutic approaches with important effects on disease outcome.

Acknowledgments

This research was supported in part by the National Science Foundation of China (Grant Nos. 81172276, 81370065 and 81372653).

References

[1] A. Jemal, F. Bray, M.M. Center, J. Ferlay, E. Ward, D. Forman, Global cancer statistics, CA Cancer J. Clin. 61 (2011) 69–90.
[2] M. Hidalgo, Pancreatic cancer, N. Engl. J. Med. 362 (2010) 1605–1617.
[3] R. Siegel, D. Naishadham, A. Jemal, Cancer statistics, 2013, CA Cancer J. Clin. 63 (2013) 11–30.
[4] C.L. Wolfgang, J.M. Herman, D.A. Laheru, A.P. Klein, M.A. Erdek, E.K. Fishman, R.H. Hruban, Recent progress in pancreatic cancer, CA Cancer J. Clin. 63 (2013) 318–348.
[5] G. Foltz, G.Y. Ryu, J.G. Yoon, T. Nelson, J. Fahey, A. Frakes, H. Lee, L. Field, K. Zander, Z. Sibenaller, T.C. Ryken, R. Vibhakar, L. Hood, A. Madan, Genome-wide analysis of epigenetic silencing identifies BEX1 and BEX2 as candidate tumor suppressor genes in malignant glioma, Cancer Res. 66 (2006) 6665–6674.
[6] J. Chien, K. Narita, R. Rattan, S. Giri, R. Shridhar, J. Staub, D. Beleford, J. Lai, L.R. Roberts, J. Molina, S.H. Kaufmann, G.C. Prendergast, V. Shridhar, A role for candidate tumor-suppressor gene TCEAL7 in the regulation of c-Myc activity, cyclin D1 levels and cellular transformation, Oncogene 27 (2008) 7223–7234.
[7] R. Rattan, K. Narita, J. Chien, J.L. Maguire, R. Shridhar, S. Giri, V. Shridhar, TCEAL7, a putative tumor suppressor gene, negatively regulates NF-kappaB pathway, Oncogene 29 (2010) 1362–1373.
[8] Z. Guo, J. Yuan, W. Tang, X. Chen, X. Gu, K. Luo, Y. Wang, B. Wan, L. Yu, Cloning and characterization of the human gene RAP2C, a novel member of Ras family, which activates transcriptional activities of SRE, Mol. Biol. Rep. 34 (2007) 137–144.
[9] A. Singh, P. Greninger, D. Rhodes, L. Koopman, S. Violette, N. Bardeesy, J. Settleman, A gene expression signature associated with "K-Ras addiction" reveals regulators of EMT and tumor cell survival, Cancer Cell 15 (2009) 489–500.
[10] D.C. Voon, H. Wang, J.K. Koo, J.H. Chai, Y.T. Hor, T.Z. Tan, Y.S. Chu, S. Mori, Y. Ito, EMT-induced stemness and tumorigenicity are fueled by the EGFR/Ras pathway, PLoS One 8 (2013) e70427.
[11] Z. Wang, S. Ali, S. Banerjee, B. Bao, Y. Li, A.S. Azmi, M. Korc, F.H. Sarkar, Activated K-Ras and INK4a/Arf deficiency promote aggressiveness of pancreatic cancer by induction of EMT consistent with cancer stem cell phenotype, J. Cell. Physiol. 228 (2013) 556–562.
[12] J. Espada, S. Galaz, F. Sanz-Rodriguez, A. Blazquez-Castro, J.C. Stockert, L. Bagazgoitia, P. Jaen, S. Gonzalez, A. Cano, A. Juarranz, Oncogenic H-Ras and PI3K signaling can inhibit E-cadherin-dependent apoptosis and promote cell survival after photodynamic therapy in mouse keratinocytes, J. Cell. Physiol. 219 (2009) 84–93.
[13] M.P. di Magliano, C.D. Logsdon, Roles for KRAS in pancreatic tumor development and progression, Gastroenterology 144 (2013) 1220–1229.
[14] G. Zimmermann, B. Papke, S. Ismail, N. Vartak, A. Chandra, M. Hoffmann, S.A. Hahn, G. Triola, A. Wittinghofer, P.I. Bastiaens, H. Waldmann, Small molecule inhibition of the KRAS–PDEdelta interaction impairs oncogenic KRAS signalling, Nature 497 (2013) 638–642.
[15] K. Polyak, R.A. Weinberg, Transitions between epithelial and mesenchymal states: acquisition of malignant and stem cell traits, Nat. Rev. Cancer 9 (2009) 265–273.
[16] D.J. Birnbaum, E. Mamessier, D. Birnbaum, The emerging role of the TGFbeta tumor suppressor pathway in pancreatic cancer, Cell Cycle 11 (2012) 683–686.
[17] Y. Katsuno, S. Lamouille, R. Derynck, TGF-beta signaling and epithelial–mesenchymal transition in cancer progression, Curr. Opin. Oncol. 25 (2013) 76–84.
[18] N. Bardeesy, K.H. Cheng, J.H. Berger, G.C. Chu, J. Pahler, P. Olson, A.F. Hezel, J. Horner, G.Y. Lauwers, D. Hanahan, R.A. DePinho, Smad4 is dispensable for normal pancreas development yet critical in progression and tumor biology of pancreas cancer, Genes Dev. 20 (2006) 3130–3146.
[19] J.A. Castellanos, N.B. Merchant, N.S. Nagathihalli, Emerging targets in pancreatic cancer: epithelial–mesenchymal transition and cancer stem cells, Onco Targets Ther. 6 (2013) 1261–1267.
[20] S.A. Mani, W. Guo, M.J. Liao, E.N. Eaton, A. Ayyanan, A.Y. Zhou, M. Brooks, F. Reinhard, C.C. Zhang, M. Shipitsin, L.L. Campbell, K. Polyak, C. Brisken, J. Yang, R.A. Weinberg, The epithelial–mesenchymal transition generates cells with properties of stem cells, Cell 133 (2008) 704–715.
[21] Z. Wang, Y. Li, D. Kong, S. Banerjee, A. Ahmad, A.S. Azmi, S. Ali, J.L. Abbruzzese, G.E. Gallick, F.H. Sarkar, Acquisition of epithelial–mesenchymal transition phenotype of gemcitabine-resistant pancreatic cancer cells is linked with activation of the notch signaling pathway, Cancer Res. 69 (2009) 2400–2407.
[22] J.P.t. Morris, S.C. Wang, M. Hebrok, KRAS, Hedgehog, Wnt and the twisted developmental biology of pancreatic ductal adenocarcinoma, Nat. Rev. Cancer 10 (2010) 683–695.
[23] U. Wellner, J. Schubert, U.C. Burk, O. Schmalhofer, F. Zhu, A. Sonntag, B. Waldvogel, C. Vannier, D. Darling, A. zur Hausen, V.G. Brunton, J. Morton, O. Sansom, J. Schuler, M.P. Stemmler, C. Herzberger, U. Hopt, T. Keck, S. Brabletz, T. Brabletz, The EMT-activator ZEB1 promotes tumorigenicity by repressing stemness-inhibiting microRNAs, Nat. Cell Biol. 11 (2009) 1487–1495.
[24] Y. Li, T.G. VandenBoom II, D. Kong, Z. Wang, S. Ali, P.A. Philip, F.H. Sarkar, Up-regulation of miR-200 and let-7 by natural agents leads to the reversal of epithelial-to-mesenchymal transition in gemcitabine-resistant pancreatic cancer cells, Cancer Res. 69 (2009) 6704–6712.
[25] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[26] H. Acloque, M.S. Adams, K. Fishwick, M. Bronner-Fraser, M.A. Nieto, Epithelial–mesenchymal transitions: the importance of changing cell state in development and disease, J. Clin. Invest. 119 (2009) 1438–1449.
[27] R. Kalluri, R.A. Weinberg, The basics of epithelial–mesenchymal transition, J. Clin. Invest. 119 (2009) 1420–1428.
[28] J.P. Thiery, H. Acloque, R.Y. Huang, M.A. Nieto, Epithelial–mesenchymal transitions in development and disease, Cell 139 (2009) 871–890.
[29] J.P. Thiery, J.P. Sleeman, Complex networks orchestrate epithelial–mesenchymal transitions, Nat. Rev. Mol. Cell Biol. 7 (2006) 131–142.

[30] S.M. Hong, A. Li, K. Olino, C.L. Wolfgang, J.M. Herman, R.D. Schulick, C. Iacobuzio-Donahue, R.H. Hruban, M. Goggins, Loss of E-cadherin expression and outcome among patients with resectable pancreatic adenocarcinomas, Mod. Pathol. 24 (2011) 1237–1247.
[31] J. von Burstin, S. Eser, M.C. Paul, B. Seidler, M. Brandl, M. Messer, A. von Werder, A. Schmidt, J. Mages, P. Pagel, A. Schnieke, R.M. Schmid, G. Schneider, D. Saur, E-cadherin regulates metastasis of pancreatic cancer in vivo and is suppressed by a SNAIL/HDAC1/HDAC2 repressor complex, Gastroenterology 137 (2009) 361–371 (371 e361–365).
[32] O. Schmalhofer, S. Brabletz, T. Brabletz, E-cadherin, beta-catenin, and ZEB1 in malignant progression of cancer, Cancer Metastasis Rev. 28 (2009) 151–166.
[33] G. Strathdee, Epigenetic versus genetic alterations in the inactivation of E-cadherin, Semin. Cancer Biol. 12 (2002) 373–379.
[34] G. Christofori, New signals from the invasive front, Nature 441 (2006) 444–450.
[35] J. Xu, W. Zhu, W. Xu, W. Yao, B. Zhang, Y. Xu, S. Ji, C. Liu, J. Long, Q. Ni, X. Yu, Up-regulation of MBD1 promotes pancreatic cancer cell epithelial–mesenchymal transition and invasion by epigenetic down-regulation of E-cadherin, Curr. Mol. Med. 13 (2013) 387–400.
[36] H. Peinado, D. Olmeda, A. Cano, Snail, Zeb and bHLH factors in tumour progression: an alliance against the epithelial phenotype? Nat. Rev. Cancer 7 (2007) 415–428.
[37] B. Hotz, M. Arndt, S. Dullat, S. Bhargava, H.J. Buhr, H.G. Hotz, Epithelial to mesenchymal transition: expression of the regulators snail, slug, and twist in pancreatic cancer, Clin. Cancer Res. 13 (2007) 4769–4776.
[38] M.A. Shields, S.B. Krantz, D.J. Bentrem, S. Dangi-Garimella, H.G. Munshi, Interplay between beta1-integrin and Rho signaling regulates differential scattering and motility of pancreatic cancer cells by snail and Slug proteins, J. Biol. Chem. 287 (2012) 6218–6229.
[39] C. Kudo-Saito, H. Shirako, T. Takeuchi, Y. Kawakami, Cancer metastasis is accelerated through immunosuppression during Snail-induced EMT of cancer cells, Cancer Cell 15 (2009) 195–206.
[40] A. Aghdassi, M. Sendler, A. Guenther, J. Mayerle, C.O. Behn, C.D. Heidecke, H. Friess, M. Buchler, M. Evert, M.M. Lerch, F.U. Weiss, Recruitment of histone deacetylases HDAC1 and HDAC2 by the transcriptional repressor ZEB1 downregulates E-cadherin expression in pancreatic cancer, Gut 61 (2012) 439–448.
[41] I. Gukovsky, N. Li, J. Todoric, A. Gukovskaya, M. Karin, Inflammation, autophagy, and obesity: common features in the pathogenesis of pancreatitis and pancreatic cancer, Gastroenterology 144 (2013) 1199–1209 (e1194).
[42] A. Neesse, P. Michl, K.K. Frese, C. Feig, N. Cook, M.A. Jacobetz, M.P. Lolkema, M. Buchholz, K.P. Olive, T.M. Gress, D.A. Tuveson, Stromal biology and therapy in pancreatic cancer, Gut 60 (2011) 861–868.
[43] M. Erkan, S. Hausmann, C.W. Michalski, A.A. Fingerle, M. Dobritz, J. Kleeff, H. Friess, The role of stroma in pancreatic cancer: diagnostic and therapeutic implications, Nat. Rev. Gastroenterol. Hepatol. 9 (2012) 454–467.
[44] C. Franci, M. Takkunen, N. Dave, F. Alameda, S. Gomez, R. Rodriguez, M. Escriva, B. Montserrat-Sentis, T. Baro, M. Garrido, F. Bonilla, I. Virtanen, A. Garcia de Herreros, Expression of Snail protein in tumor–stroma interface, Oncogene 25 (2006) 5134–5144.
[45] M. Erkan, C. Reiser-Erkan, C.W. Michalski, J. Kleeff, Tumor microenvironment and progression of pancreatic cancer, Exp. Oncol. 32 (2010) 128–131.
[46] G. Luo, J. Long, B. Zhang, C. Liu, J. Xu, Q. Ni, X. Yu, Stroma and pancreatic ductal adenocarcinoma: an interaction loop, Biochim. Biophys. Acta 1826 (2012) 170–178.
[47] A.D. Rhim, P.E. Oberstein, D.H. Thomas, E.T. Mirek, C.F. Palermo, S.A. Sastra, E.N. Dekleva, T. Saunders, C.P. Becerra, I.W. Tattersall, C.B. Westphalen, J. Kitajewski, M.G. Fernandez-Barrena, M.E. Fernandez-Zapico, C. Iacobuzio-Donahue, K.P. Olive, B.Z. Stanger, Stromal elements act to restrain, rather than support, pancreatic ductal adenocarcinoma, Cancer Cell 25 (2014) 735–747.
[48] B.C. Ozdemir, T. Pentcheva-Hoang, J.L. Carstens, X. Zheng, C.C. Wu, T.R. Simpson, H. Laklai, H. Sugimoto, C. Kahlert, S.V. Novitskiy, A. De Jesus-Acosta, P. Sharma, P. Heidari, U. Mahmood, L. Chin, H.L. Moses, V.M. Weaver, A. Maitra, J.P. Allison, V.S. LeBleu, R. Kalluri, Depletion of carcinoma-associated fibroblasts and fibrosis induces immunosuppression and accelerates pancreas cancer with reduced survival, Cancer Cell 25 (2014) 719–734.
[49] J.J. Lee, R.M. Perera, H. Wang, D.C. Wu, X.S. Liu, S. Han, J. Fitamant, P.D. Jones, K.S. Ghanta, S. Kawano, J.M. Nagle, V. Deshpande, Y. Boucher, T. Kato, J.K. Chen, J.K. Willmann, N. Bardeesy, P.A. Beachy, Stromal response to Hedgehog signaling restrains pancreatic cancer progression, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) E3091–E3100.
[50] C. Feig, A. Gopinathan, A. Neesse, D.S. Chan, N. Cook, D.A. Tuveson, The pancreas cancer microenvironment, Clin. Cancer Res. 18 (2012) 4266–4276.
[51] S.I. Grivennikov, F.R. Greten, M. Karin, Immunity, inflammation, and cancer, Cell 140 (2010) 883–899.
[52] S.I. Grivennikov, M. Karin, Inflammation and oncogenesis: a vicious connection, Curr. Opin. Genet. Dev. 20 (2010) 65–71.
[53] J. Yang, R.A. Weinberg, Epithelial–mesenchymal transition: at the crossroads of development and tumor metastasis, Dev. Cell 14 (2008) 818–829.
[54] A.D. Rhim, E.T. Mirek, N.M. Aiello, A. Maitra, J.M. Bailey, F. McAllister, M. Reichert, G.L. Beatty, A.K. Rustgi, R.H. Vonderheide, S.D. Leach, B.Z. Stanger, EMT and dissemination precede pancreatic tumor formation, Cell 148 (2012) 349–361.
[55] S. Shi, W. Yao, J. Xu, J. Long, C. Liu, X. Yu, Combinational therapy: new hope for pancreatic cancer? Cancer Lett. 317 (2012) 127–135.
[56] S. Etienne-Manneville, Microtubules in cell migration, Annu. Rev. Cell Dev. Biol. 29 (2013) 471–499.
[57] N. Li, P. Jiang, W. Du, Z. Wu, C. Li, M. Qiao, X. Yang, M. Wu, Siva1 suppresses epithelial–mesenchymal transition and metastasis of tumor cells by inhibiting stathmin and stabilizing microtubules, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 12851–12856.
[58] Y. Nakaya, E.W. Sukowati, Y. Wu, G. Sheng, RhoA and microtubule dynamics control cell–basement membrane interaction in EMT during gastrulation, Nat. Cell Biol. 10 (2008) 765–775.
[59] L. Jiang, Y. Chen, C.Y. Chan, X. Wang, L. Lin, M.L. He, M.C. Lin, D.T. Yew, J.J. Sung, J.C. Li, H.F. Kung, Down-regulation of stathmin is required for TGF-beta inducible early gene 1 induced growth inhibition of pancreatic cancer cells, Cancer Lett. 274 (2009) 101–108.
[60] S. Yamada, B.C. Fuchs, T. Fujii, Y. Shimoyama, H. Sugimoto, S. Nomoto, S. Takeda, K.K. Tanabe, Y. Kodera, A. Nakao, Epithelial-to-mesenchymal transition predicts prognosis of pancreatic cancer, Surgery 154 (2013) 946–954.
[61] Y. Li, D. Kong, A. Ahmad, B. Bao, F.H. Sarkar, Pancreatic cancer stem cells: emerging target for designing novel therapy, Cancer Lett. 338 (2013) 94–100.
[62] T. Shimamura, M. Sakamoto, Y. Ino, Y. Sato, K. Shimada, T. Kosuge, H. Sekihara, S. Hirohashi, Dysadherin overexpression in pancreatic ductal adenocarcinoma reflects tumor aggressiveness: relationship to e-cadherin expression, J. Clin. Oncol. 21 (2003) 659–667.
[63] D. Ansari, A. Rosendahl, J. Elebro, R. Andersson, Systematic review of immunohistochemical biomarkers to identify prognostic subgroups of patients with pancreatic cancer, Br. J. Surg. 98 (2011) 1041–1055.
[64] T. Yin, C. Wang, T. Liu, G. Zhao, Y. Zha, M. Yang, Expression of snail in pancreatic cancer promotes metastasis and chemoresistance, J. Surg. Res. 141 (2007) 196–203.
[65] T. Arumugam, V. Ramachandran, K.F. Fournier, H. Wang, L. Marquis, J.L. Abbruzzese, G.E. Gallick, C.D. Logsdon, D.J. McConkey, W. Choi, Epithelial to mesenchymal transition contributes to drug resistance in pancreatic cancer, Cancer Res. 69 (2009) 5820–5828.
[66] O. Khan, N.B. La Thangue, HDAC inhibitors in cancer biology: emerging mechanisms and clinical applications, Immunol. Cell Biol. 90 (2012) 85–94.
[67] R.F. Hwang, T. Moore, T. Arumugam, V. Ramachandran, K.D. Amos, A. Rivera, B. Ji, D.B. Evans, C.D. Logsdon, Cancer-associated stromal fibroblasts promote pancreatic tumor progression, Cancer Res. 68 (2008) 918–926.
[68] S. Hamada, A. Masamune, T. Shimosegawa, Novel therapeutic strategies targeting tumor–stromal interactions in pancreatic cancer, Front. Physiol. 4 (2013) 331.
[69] K.P. Olive, M.A. Jacobetz, C.J. Davidson, A. Gopinathan, D. McIntyre, D. Honess, B. Madhu, M.A. Goldgraben, M.E. Caldwell, D. Allard, K.K. Frese, G. Denicola, C. Feig, C. Combs, S.P. Winter, H. Ireland-Zecchini, S. Reichelt, W.J. Howat, A. Chang, M. Dhara, L. Wang, F. Ruckert, R. Grutzmann, C. Pilarsky, K. Izeradjene, S.R. Hingorani, P. Huang, S.E. Davies, W. Plunkett, M. Egorin, R.H. Hruban, N. Whitebread, K. McGovern, J. Adams, C. Iacobuzio-Donahue, J. Griffiths, D.A. Tuveson, Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer, Science 324 (2009) 1457–1461.
[70] Z. Wang, Y. Li, A. Ahmad, S. Banerjee, A.S. Azmi, D. Kong, F.H. Sarkar, Pancreatic cancer: understanding and overcoming chemoresistance, Nat. Rev. Gastroenterol. Hepatol. 8 (2011) 27–33.
[71] C. Liu, H. Cheng, S. Shi, X. Cui, J. Yang, L. Chen, P. Cen, X. Cai, Y. Lu, C. Wu, W. Yao, Y. Qin, L. Liu, J. Long, J. Xu, M. Li, X. Yu, MicroRNA-34b inhibits pancreatic cancer metastasis through repressing Smad3, Curr. Mol. Med. 13 (2013) 467–478.
[72] S. Ali, A. Ahmad, S. Banerjee, S. Padhye, K. Dominiak, J.M. Schaffert, Z. Wang, P.A. Philip, F.H. Sarkar, Gemcitabine sensitivity can be induced in pancreatic cancer cells through modulation of miR-200 and miR-21 expression by curcumin or its analogue CDF, Cancer Res. 70 (2010) 3606–3617.
[73] D.M. Gonzalez, D. Medici, Signaling mechanisms of the epithelial–mesenchymal transition, Sci. Signal. 7 (2014) re8.
[74] M. Korpal, B.J. Ell, F.M. Buffa, T. Ibrahim, M.A. Blanco, T. Celia-Terrassa, L. Mercatali, Z. Khan, H. Goodarzi, Y. Hua, Y. Wei, G. Hu, B.A. Garcia, J. Ragoussis, D. Amadori, A.L. Harris, Y. Kang, Direct targeting of Sec23a by miR-200s influences cancer cell secretome and promotes metastatic colonization, Nat. Med. 17 (2011) 1101–1108.
[75] N.Y. Lin, C. Beyer, A. Giessl, T. Kireva, C. Scholtysek, S. Uderhardt, L.E. Munoz, C. Dees, A. Distler, S. Wirtz, G. Kronke, B. Spencer, O. Distler, G. Schett, J.H. Distler, Autophagy regulates TNFalpha-mediated joint destruction in experimental arthritis, Ann. Rheum. Dis. 72 (2013) 761–768.
[76] I. Akalay, B. Janji, M. Hasmim, M.Z. Noman, J.P. Thiery, F. Mami-Chouaib, S. Chouaib, EMT impairs breast carcinoma cell susceptibility to CTL-mediated lysis through autophagy induction, Autophagy 9 (2013) 1104–1106.
[77] I. Akalay, B. Janji, M. Hasmim, M.Z. Noman, F. Andre, P. De Cremoux, P. Bertheau, C. Badoual, P. Vielh, A.K. Larsen, M. Sabbah, T.Z. Tan, J.H. Keira, N.T. Hung, J.P. Thiery, F. Mami-Chouaib, S. Chouaib, Epithelial-to-mesenchymal transition and autophagy induction in breast carcinoma promote escape from T-cell-mediated lysis, Cancer Res. 73 (2013) 2418–2427.
[78] J. Li, B. Yang, Q. Zhou, Y. Wu, D. Shang, Y. Guo, Z. Song, Q. Zheng, J. Xiong, Autophagy promotes hepatocellular carcinoma cell invasion through activation of epithelial–mesenchymal transition, Carcinogenesis 34 (2013) 1343–1351.
[79] L. Qiang, Y.Y. He, Autophagy deficiency stabilizes TWIST1 to promote epithelial–mesenchymal transition, Autophagy 10 (2014) 1864–1865.
[80] H. Cheng, J. Li, C. Liu, W. Yao, Y. Xu, T.S. Frank, X. Cai, S. Shi, Y. Lu, Y. Qin, L. Liu, J. Xu, J. Long, Q.X. Ni, M. Li, X.J. Yu, Profilin1 sensitizes pancreatic cancer cells to irradiation by inducing apoptosis and reducing autophagy, Curr. Mol. Med. 13 (2013) 1368–1375.