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Review

Carcinosarcomas: tumors in transition?

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Summary. Carcinosarcomas are rare, biphasic tumors that are comprised of carcinomatous and sarcomatous elements. While the exact mechanism by which these two phenotypes arise within a single tumor remains unclear, molecular evidence indicates that the epitheliod and spindle-cell components share a clonal origin. We propose that the biphasic nature of these neoplasms may represent an extreme case of epithelial plasticity, in which an epithelial-like cell undergoes a transition to a more mesenchymal phenotype. The present review will discuss both the histological and molecular biological evidence of the involvement of epithelial plasticity in driving the mixed phenotypes observed in carcinosarcomas.

Key words: Epithelial-mesenchymal transition, Mesenchymal-epithelial transition, Sarcomatoid carcinoma, EMT, MET

Introduction

Carcinosarcoma (CS) is a rare but highly malignant tumor composed of both epithelial (carcinomatous) and mesenchymal (sarcomatous) components. These biphasic tumors have been reported to develop in numerous sites within the body; however, despite this anatomic diversity of origin, these tumors share several clinical features, most importantly a highly aggressive course (Nielsen et al., 1989; Hansel and Epstein, 2006; Cantrell and Van Le, 2009; Li et al., 2014). For example, in one study, 94% of sarcomatous elements within uterine CS tumors were grade IV, and 30% of uterine CS patients had metastases at the time of diagnosis (Nordal et al., 1997). In addition, even with local and systemic therapy, prognosis is poor due to very high rates of local tumor recurrence and distant metastases (Hansel and Epstein, 2006; Cantrell et al., 2012; Li et al., 2014). Given the rarity of CS, attempts to conduct prospective trials to improve therapeutic outcomes for patients have been difficult. Management of CS has been mostly guided by published, retrospective studies, case reports, and anecdotal experience.

Although CS remains poorly studied, there is some evidence that epithelial plasticity plays a role in driving the biphasic nature of these neoplasms. Epithelial plasticity, as defined here, is the conversion of a cell from an epithelial-like to a mesenchymal-like phenotype and vice versa. Epithelial plasticity includes classic transitions, such as epithelial-mesenchymal transitions (EMT) and mesenchymal-epithelial transitions (MET) (reviewed in (Bitting et al., 2014)); however, other conversions linked with phenotypic plasticity may also include mesenchymal-amoeboid transitions (Morley et al., 2014), epithelial-endothelial transitions (vasculogenic mimicry (Zhang et al., 2007)), and epithelial-osseous transitions (osteomimicry (Rucci and Teti, 2010)). While many EMT/MET events have been

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shown to be reversible (Thomson et al., 2011; Tsai et al., 2012), other phenotypic transitions may become fixed via epigenetic or genetic mechanisms (Dumont et al., 2008; Thomson et al., 2011). Epithelial plasticity confers upon cells specific phenotypic traits that facilitate progression along the metastatic cascade. For example, EMT within primary carcinomas lead to loss of epithelial-specific cell-cell adhesion and a gain in invasive capacity (reviewed in (Bitting et al., 2014)). EMT is also usually accompanied by a downregulation of proliferative signals, and a reversion back to an epithelial phenotype via MET is postulated to restore proliferation upon metastatic colonization (Brabletz et al., 2001; Vega et al., 2004; Tsai et al., 2012). Interestingly, epithelial plasticity is not unique to carcinomas, and phenotypic conversions also seem to be a feature of mesenchymally-derived sarcomas (reviewed in (Yang et al., 2014)). In fact, these transitions may have prognostic value in sarcoma. For example, histological analyses of clinical sarcoma specimens indicate that expression of the epithelial biomarker, E-cadherin, within sarcomas is prognostic for better overall survival (Yin et al., 2012; Tian et al., 2013). CS is a unique cancer subtype with both epithelial-like and mesenchymal-like components. These cancers may represent a rare example of epithelial plasticity in which many cells within the primary tumor have undergone phenotypic transitions.

In this review, we aim to link the current clinical challenges of CS treatment to the underlying cancer biology and genetics of these tumor types. We begin by briefly summarizing the clinical characteristics and management of CS in selected tissues of origin, including uterine, ovarian, renal, and prostate, to provide a general background of the highly malignant nature of these tumors. For information on other types of CS, Table 1 features current details regarding prognostic factors, therapeutic options, survival data, and selected references. Following the clinical review, we then discuss the histological and molecular evidence that

Table 1. Additional CS tumor characteristics.

CS Type	Prognostic Factors	Therapeutic Options	Survival	Selected References
Uterine	Stage, grade, tumor size and location, cell type (heterologous), invasion into lymphovascular space, depth of invasion	Surgery; Adjuvant radiation; Adjuvant chemotherapy (platinum drugs, taxanes, ifosfamide)	Five year survival: Stage I-II: 59%; Stage III: 22%; Stage IV: 9%	Gonzalez Bosquet et al., 2010; Nordal et al., 1997; Yamada et al., 2000
Ovarian	Stage, cell type (heterologous)	Surgery; Adjuvant radiation therapy; Adjuvant chemotherapy (platinum drugs, paclitaxel, ifosfamide, doxorubicin, dacarbazine)	Five year survival: 7.5%	del Carmen et al., 2012; Harris et al., 2003
Prostate	Not available	Surgery; Radiation therapy; Hormone therapy; Chemotherapy	Five year survival: 41%	Fukawa et al., 2003; Hansel et al., 2007
Breast	Not available	Surgery: Lumpectomy or mastectomy with axillary lymph node dissection; Adjuvant chemotherapy: anthracycline/taxane; cyclophosphamide, methotrexate, 5-fluorouracil; Adjuvant radiation therapy; Additional adjuvant therapy (if receptor (+)): adjuvant hormone therapy; monoclonal antibodies and small molecule inhibitors	Five year survival: 49%	Tian and Xu, 2012; Gogas et al., 2003; Tokudome et al., 2004
Urinary Bladder	Pathological stage, surgical margins, metastatic disease at presentation	Surgery: Transurethral resection and partial cystectomy or radical cystectomy with pelvic lymphadenectomy; Adjuvant chemotherapy: gemcitabine, cisplatin, methotrexate, vinblastine, doxorubicin, cisplatin, ifosfamide; Adjuvant radiation therapy	Five year survival: 28.4-37%	Bansal et al., 2013; Wang et al., 2010
Lung	Tumor size	Surgery; Concurrent or adjuvant chemotherapy: cisplatin, vinorelbine; Adjuvant radiation therapy	Five year survival: 12-21%	Sakukra et al., 2014; Koss et al., 1999
Cutaneous	Epithelial component, age, tumor size, recent tumor growth, regional lymph node involvement, history of tumor duration	Surgery; Adjuvant radiotherapy; Adjuvant chemotherapy	Five year survival: Epidermal-derived 70%; Adnexal 25%	Hong et al., 2013; Tran et al., 2005; El Harroudi et al., 2010
Liver	Not available	Surgery: Segmentectomy or hepatectomy; Additional local therapies: transarterial chemoembolization; percutaneous ethanol injection; percutaneous microwave ablation; Adjuvant chemotherapy; Radiation therapy: adjuvant; regional lymph node RT	Three year survival post-surgery: 9%	Wang et al., 2012; Lao et al., 2007
Salivary Gland	Not available	Surgery; Adjuvant radiation therapy; Adjuvant chemotherapy	Median survival time=3.6 years	Taki et al., 2013; Staffieri et al., 2007
Gastric	Not available	Surgery: Partial or total gastrectomy with lymph node dissection; Adjuvant chemotherapy; Adjuvant radiation therapy	Median survival time =10-15 months	Randjelovic et al., 2007; Teramachi et al., 2003

epithelial plasticity is responsible for driving the biphasic phenotype observed in CS.

Clinical characteristics of carcinosarcoma

Malignant mixed Müllerian tumors: Uterine and ovarian carcinosarcoma

Uterine Carcinosarcoma

Uterine CS has an incidence of fewer than three cases per 100,000 women per year, and these neoplasms represent approximately 4% of all uterine cancers (Siegel et al., 2013). Women over the age of 65 account for nearly 50% of diagnosed uterine CS in the United States (Leath III et al., 2009). The carcinomatous component of uterine CS is usually of the endometriod type, but it may also be serous, clear cell, or squamous. The sarcomatous component may be derived from homologous tissue, such as endometrial stromal sarcoma, fibrosarcoma, or leiomyosarcoma, or it may be derived from heterologous tissue, such as rhabdomyosarcoma, chondrosarcoma, osteosarcoma, or liposarcoma (Jin et al., 2003). Previously, uterine CS had been classified as a type of uterine sarcoma; however, there is continued debate about whether CS is more similar to poorly differentiated endometrial carcinomas than other uterine sarcomas (McCluggage, 2002a). For example, studies have found that the behavior and overall prognosis of uterine CS is more dependent on the characteristics of the epithelial than the stromal elements (Silverberg et al., 1990; Nordal et al., 1997). In cases where the epithelial element is grade III endometrioid, serous, or clear cell in type, there is a higher frequency of metastasis (Silverberg et al., 1990; Nordal et al., 1997).

Approximately 35 to 44% of patients with uterine CS present with advanced-stage disease (Stage III or IV) at the time of diagnosis (Nielsen et al., 1989; Gonzalez Bosquet et al., 2010; Li et al., 2014). In addition, recurrence rates for uterine CS are approximately 50% (Leath III et al., 2009), and, despite treatment, the five-year survival rate is poor (Stage I-II: 59%, Stage III: 22%, Stage IV: 9%) (Gonzalez Bosquet et al., 2010). In comparison, the majority of women diagnosed with endometrial adenocarcinoma (approximately 70%) have early-stage disease (International Federation of Gynecology and Obstetrics (FIGO) Stages I and II) (SEER Cancer Statistics Review 1975-2008; Data 2001-2007), and the five-year survival rates for endometrial adenocarcinoma in the US by FIGO stage are Stage I-II: 69-88%, Stage III: 47-58%, and Stage IV: 15-17% (American Cancer Society – last revised 2/3/2014). The reduced survival rates for uterine CS are due to the high propensity for both local and distant tumor recurrence (Dinh et al., 1989; Nielsen et al., 1989; Wolfson et al., 2007; Gonzalez Bosquet et al., 2010). Poor prognostic factors include stage, grade, tumor size and location, presence of heterologous elements, invasion into the lymphovascular space, and depth of invasion (Major et al., 1993; Yamada et al., 2000).

Treatment for uterine CS may involve a combination of local and systemic therapy (Manolitsas et al., 2001; Gonzalez Bosquet et al., 2010; Li et al., 2014). Surgery is the primary local treatment; however, local therapeutic options can also include interstitial radiation and adjuvant external beam pelvic irradiation. The efficacy of adjuvant pelvic radiation in patients with early stage uterine CS was evaluated in a randomized, controlled trial conducted by the European Organization for Research and Treatment of Cancer (Reed et al., 2008). Adjuvant pelvic radiation was associated with a significantly reduced risk of pelvic recurrence in patients with uterine CS, but this treatment had no significant impact on either progression-free or overall survival in these patients (Reed et al., 2008). Vaginal brachytherapy has also been utilized as a local therapy for uterine CS (Nout et al., 2009; Li et al., 2014). In a retrospective analysis, the combination of surgery and adjuvant radiation therapy with or without chemotherapy was seen to improve overall survival compared to surgery alone for patients with uterine CS confined to the pelvis (Li et al., 2014).

Because most patients' treatment failures are due to the development of distant metastases, systemic therapy is often prescribed. The National Comprehensive Cancer Network guidelines recommend adjuvant chemotherapy as a treatment option in patients diagnosed with early-stage uterine CS (Greer et al., 2009). Indeed, most patients with uterine CS are treated with various combinations of chemotherapeutics, including platinum drugs, taxanes, and ifosfamide (Sutton et al., 2000; Homesley et al., 2007; Hoskins et al., 2008; El-Nashar and Mariani, 2011; Garg et al., 2014); however, multiple studies have found that adjuvant chemotherapy is not associated with a significant improvement in overall survival in patients with early-stage uterine CS (Omura et al., 1983; Wolfson et al., 2007; Cantrell et al., 2012; Garg et al., 2014).

Neither local nor systemic adjuvant therapy has been shown to be superior compared to the other in improving therapeutic outcome for patients with uterine CS. In 2007, the results from the largest prospective trial assessing adjuvant therapy in uterine CS were reported (Wolfson et al., 2007). This trial compared adjuvant whole abdominal irradiation to chemotherapy following primary surgery for women with uterine CS. There was no significant difference in survival between the two arms.

Ovarian Carcinosarcoma

CS of the ovary accounts for less than 1% of all ovarian cancers, and they are generally diagnosed in postmenopausal women (Harris et al., 2003). Typically, the diagnosis of CS is based on pathological analysis of morphology. In cases for which the tumor is purely mesenchymal in appearance, but does not have the

morphology of a typical sarcoma (i.e. long sweeping bundles typical of leiomyosarcoma), immunohistochemistry (IHC) for an epithelial marker, such as keratin, helps to diagnose CS. In addition, the pathologist must exclude sarcomas that can express keratin (e.g. epithelioid sarcoma or epithelioid angiosarcoma) based on morphology and the site where the tumor is arising. CS of ovarian or uterine origin is also distinguished by positive CK7 and negative CK20 staining, while IHC for desmin and smooth muscle actin aid in ruling out strict sarcomas of smooth muscle origin (reviewed in del Carmen et al., 2012).

The strongest prognostic factor for ovarian CS is stage of disease (Cicin et al., 2008), although there have been conflicting reports regarding the prognostic significance of the histopathologic characteristics of the tissue (reviewed in del Carmen et al., 2012). The epithelial component of ovarian CS is often serous, endometroid, or undifferentiated adenocarcinoma, but it may also be clear cell adenocarcinoma or squamous cell carcinoma (del Carmen et al., 2012). The sarcomatous element may be homologous tissue, such as endometrial stromal sarcoma, fibrosarcoma, or leiomyosarcoma, or heterologous tissue, including chondrosarcoma, rhabdomyosarcoma, or osteosarcoma (del Carmen et al., 2012). Two cases of ovarian CS with neuroendocrine differentiation in the epithelial component have also been reported (Lim et al., 1998; Dittus et al., 2014).

Patients who develop ovarian CS have worse outcomes compared to those with ovarian carcinoma (Rauh-Hain et al., 2011). Approximately 75% of women with CS of the ovary will present with stage III or IV disease, and in more than 90% of cases, the disease will have spread beyond the ovary at diagnosis (FIGO Stage II – IV disease) (Cantrell and Van Le, 2009). Despite therapy, the prognosis of ovarian CS is poor with an overall 5-year survival rate of 7.5% (Harris et al., 2003; Silasi et al., 2008) and median survival of 4-27 months (Harris et al., 2003; Rutledge et al., 2006). In comparison, women with all types of ovarian cancer have a five-year relative survival rate of 44% (NCI, SEER Data base 2004-2010). Most cases of malignant epithelial ovarian cancer are carcinoma (85-90%), and five-year survival rates in the US based on FIGO stage are 85-94% for Stage I, 70-78% for Stage II, 39-59% for Stage III, and 17% for Stage IV.

Local management of ovarian CS may begin with cytoreductive surgery. Although there are contradicting reports, several retrospective studies support the surgical excision of the primary ovarian CS to improve patient survival and prognosis (Brown et al., 2004; Rutledge et al., 2006; Rauh-Hain et al., 2011). Because ovarian CS is usually diagnosed at advanced stages with a high propensity to metastasize early in the course of disease, the efficacy of radiation therapy in the treatment of ovarian CS remains undefined and is largely based on anecdotal reports (Sood et al., 1998; Harris et al., 2003). Localized radiation therapy may be useful in the management of single, isolated pelvic recurrences; however, this has not been proven clinically (Mano et al., 2007; Cantrell and Van Le, 2009).

In addition to local therapies, systemic treatment with chemotherapy is common. Ovarian CS respond poorly to platinum-based chemotherapy in comparison to epithelial ovarian cancer (Brown et al., 2004; Rauh-Hain et al., 2011); however, without evidence of more effective options, patients continue to be prescribed platinum drugs as single agents or to be used in combination protocols. Treatment regimens may include platinum-based chemotherapy with or without paclitaxel, ifosfamide, or doxorubicin and dacarbazine (del Carmen et al., 2012). Reports examining the efficacy of combination chemotherapy regimens have demonstrated similar results for platinum-based chemotherapy

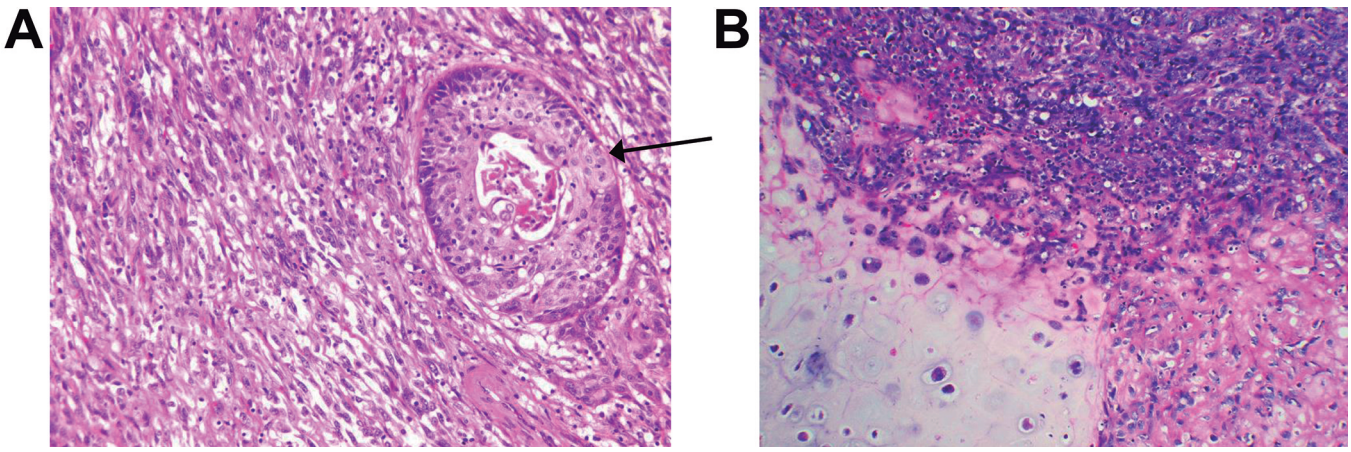

Fig. 1. Admixed carcinomatous and sarcomatous phenotypes in CS tumors. **A.** Bladder sarcomatoid carcinoma (CS) with a nest of squamous cell carcinoma (black arrow) surrounded by non-specific malignant spindle cell sarcomatous cells. **B.** Bladder sarcomatoid carcinoma (CS) with poorly differentiated carcinoma (top) and chondrosarcoma (lower left). x 200

combined with either a taxane or ifosfamide (Cicin et al., 2008).

Sarcomatoid Carcinoma of the Prostate/Prostate CS

Cases of sarcomatoid carcinoma of the prostate, (i.e. prostate CS), are infrequently reported in the literature, with fewer than 100 case reports to date (Lauwers et al., 1993; Dundore et al., 1995; Hansel and Epstein, 2006). Prostate CS tumors are comprised of both malignant glandular and spindle cell elements, whereby cases with a predominantly sarcomatoid component may be mistaken for sarcoma (Hansel et al., 2007). Sarcomatoid carcinoma of the prostate can develop with a variety of morphologic tissue patterns. The glandular regions are often comprised of either high-grade acinar adenocarcinoma or a rare subtype of prostatic carcinoma, such as small cell, foamy gland, ductal, or adenosquamous carcinoma (Hansel et al., 2007). The sarcomatoid component can make up as little as 5% of the tumor and is typically comprised of malignant spindle cells with overt atypical features, including hypercellularity, nuclear pleomorphism, frequent mitoses, and focal necrosis (Hansel et al., 2007). In approximately one-third of cases, osteosarcoma, chondrosarcoma, or rhabdomyosarcoma is observed (Hansel et al., 2007). It has not been demonstrated that there is prognostic significance to the presence of heterologous elements in sarcomatoid carcinoma of the prostate (Hansel et al., 2007). Differential diagnoses for other spindle cell lesions of the adult prostate include those unique to the prostate, such as sclerosing adenosis, stromal tumors of uncertain malignant potential (STUMP), and stromal sarcoma, and those not unique to the prostate, such as leiomyosarcoma, rhabdomyosarcoma, inflammatory myofibroblastic tumor, solitary fibrous tumor (SFT), and gastrointestinal stromal tumor (GIST) (Hansel et al., 2007). Morphologically, sarcomatoid carcinoma of the prostate is characterized by an admixture of high grade prostatic adenocarcinoma with a spindled, sarcomatoid component with variable heterologous element formation (Hansel et al., 2007).

Clinical characteristics of patients diagnosed with sarcomatoid carcinoma of the prostate include a mean age of 66 years, symptoms of urinary tract obstruction, and variable prostate-specific antigen (PSA) levels (Fukawa et al., 2003; Hansel et al., 2007). Interestingly, patients often have a prior history of developing acinar adenocarcinoma of the prostate, some cases with a delay as long as 16 years between diagnoses (Hansel et al., 2007). In one study, the majority of patients with prostatic CS had a history of adenocarcinoma treated with external beam radiation therapy, brachytherapy, or hormone therapy (Hansel and Epstein, 2006). Prognosis is poor, with 20% of patients dying within one year of diagnosis. In comparison, according to the most recent data from the National Cancer Institute when including all stages of prostate cancer, the relative five-year survival rate is almost 100% and the relative 10-year survival rate is 99%. In contrast, in one case series of patients with sarcomatoid carcinoma of the prostate, the five-year survival rate was 41% (Dundore et al., 1995). The reported survival period for patients with metastatic prostate CS is very short, approximately seven months, and the occurrence of metastatic disease was described in 64% of cases in a review of published case reports (Fukawa et al., 2003). Patients with sarcomatoid carcinoma of the prostate are prone to developing local recurrence as well as frequent widespread metastases to lung, spine or bone, lymph node, liver, and brain (Fukawa et al., 2003; Hansel and Epstein, 2006). Metastatic colonies may develop as growths of neoplastic epithelial cells, mesenchymal cells, or metastases with elements of both (Krastanova and Addonizio, 1981; Dundore et al., 1995). Various therapeutic modalities including radiotherapy, surgery, hormone therapy, and chemotherapy have been used for patients with prostatic CS, but the results have been disappointing (Fukawa et al., 2003). No prognostic parameters for prostatic CS have been identified to be predictive of outcome (Fukawa et al., 2003).

Sarcomatoid renal cell carcinoma/renal carcino-sarcoma

Sarcomatoid renal cell carcinoma, also known as renal CS, is an aggressive primary kidney cancer associated with poor prognosis. The terms carcinosarcoma of the kidney or renal pelvis and sarcomatoid renal cell carcinoma have been used interchangeably and inconsistently in various reports. According to the 2004 World Health Organization (WHO) classification of renal tumors in adults, the term "sarcomatoid renal cell carcinoma" should be used for all biphasic malignant neoplasms exhibiting morphological and/or IHC evidence of epithelial and mesenchymal differentiation (Lopez-Beltran et al., 2006). For consistency with WHO guidelines, sarcomatoid renal cell carcinoma will be used here to refer to this mixed malignant kidney cancer. The carcinomatous component of sarcomatoid renal cell carcinomas may be comprised of varying epithelial malignant tissue types, including clear cell, papillary, chromophobe, or unclassified renal cell carcinoma, transitional cell carcinoma, adenocarcinoma, or squamous cell carcinoma (reviewed in Shuch et al., 2012); the sarcomatous portion of CS tumors may contain malignant mesenchymal elements such as chondrosarcoma, osteosarcoma, rhabdomyosarcoma, lipsarcoma, and/or fibrosarcoma (reviewed in Shuch et al., 2012).

Interestingly, 5% to 10% of renal cell carcinomas (RCC) have areas of sarcomatoid morphology, and these RCC tumors with sarcomatoid elements are associated with highly malignant behavior, including increased local invasion and distant metastasis (de Peralta-Venturina et al., 2001; Cheville et al., 2004). While some studies report an association between a higher proportion of sarcomatoid tissue in the primary tumor and worse

survival (de Peralta-Venturina et al., 2001; Tickoo et al., 2007), others have refuted this observation (Mian et al., 2002; Cheville et al., 2004; Kunene et al., 2013). Additionally, the underlying histologic subtypes in sarcomatoid renal cell carcinomas have not been significantly associated with outcome among patients when analyzed in a number of studies (de Peralta-Venturina et al., 2001; Mian et al., 2002; Cheville et al., 2004).

In most published case series, the clinical presentation of patients with sarcomatoid renal cell carcinoma involves large tumors (mean size of 9-10 cm) and symptomatic disease in 90% of cases (DeLong et al., 1993; Mian et al., 2002). The incidence of metastatic disease at presentation (Stage III or IV) is very high (45-84%) (Cangiano et al., 1999; Mian et al., 2002; Cheville et al., 2004), with the most common metastatic sites reported to be lungs, bone, lymph nodes, liver, and brain (Cangiano et al., 1999). A retrospective analysis by the Mayo Clinic of cases diagnosed with sarcomatoid renal cell carcinoma via nephrectomy between 1970 and 2000 revealed a median survival following radical nephrectomy of eight months (Cheville et al., 2004). Cancer-specific survival rates at two and five years post-nephrectomy were 33.3% and 14.5%, respectively (Cheville et al., 2004). Prognostic factors significantly associated with survival in the group that underwent nephrectomy included the presence of distant metastasis at the time of surgery and histologic tumor necrosis (Cheville et al., 2004). These statistics are consistent with other reports where median survival time ranged from four to nine months after diagnosis (Mian et al., 2002; Shuch et al., 2009). These statistics can be compared to purely epithelial RCC, which is diagnosed in approximately 90% of patients with primary renal cancers (American Cancer Society – last revised 2/24/14). Approximately 60% of RCC patients present with localized (Stage I-II) disease, 15% with regional (Stage III) disease, and 25% with distant metastatic disease (Stage IV) (Kane et al., 2008). Based on data from the National Cancer Data Base (2001-2002), five-year survival rates for patients with RCC according to American Joint Comittee on Cancer (AJCC) stage are Stage I: 81%, Stage II: 74%, Stage III: 53%, and Stage 4: 8%.

Optimal therapeutic management of sarcomatoid renal cell carcinoma has not been established. Treatment outcomes for patients following nephrectomy, radiation therapy, chemotherapy, immunotherapy, and targeted therapies have been described (Cangiano et al., 1999; Cheville et al., 2004; Shuch et al., 2009; Molina et al., 2011; Shuch et al., 2012; Beuselinck et al., 2014), although nephrectomy continues to be reported as the most integral part of therapy. In the setting of metastatic sarcomatoid renal cell carcinoma, many question the survival benefit of cytoreductive surgery (Mian et al., 2002; Shuch et al., 2009, 2012). Shuch and colleagues indicated that approximately 60% of patients were not able to proceed to systemic therapy after surgery due to 1. the invasive nature of this surgery, 2. the delayed initiation of systemic therapy to allow for patient recovery, and 3. the rapid, aggressive disease progression of this cancer (Shuch et al., 2009). Currently, patients have limited systemic therapy options, and regimens have been met with very poor results (Molina et al., 2011; Shuch et al., 2012). With the goals of trying to improve therapeutic response, recent studies have investigated the utility of VEGF-targeted therapy in the treatment of sarcomatoid renal cell carcinoma (sunitinib, sorafenib, bevacizumab) (Golshayan et al., 2009; Molina et al., 2011; Kunene et al., 2013; Beuselinck et al., 2014). Median overall survival for patients in studies treated with such targeted therapies ranged from 10 to 15.7 months with partial response rates ranging from 14% to 30% (Golshayan et al., 2009; Molina et al., 2011; Kunene et al., 2013). Phase II clinical trials are underway to define the therapeutic value of the combination of chemotherapy and targeted therapies in treating sarcomatoid renal cell carcinoma (Shuch et al., 2012).

Epithelial plasticity as a driver of CS

The clinical characteristics of ovarian, uterine, prostate and renal CS were reviewed above and several additional types of CS are summarized in Table 1. It is apparent that, regardless of the site of development, CS shares an aggressive course of tumor progression, locally and distantly, and a general lack of durable response to standard therapies. What are the factors of this tumor type that makes CS so aggressive and treatment resistant? Specifically, does the biphasic and transitional nature of the tumor subtype contribute to its clinical behavior? We review the published literature of CS to discuss first the hypotheses surrounding the etiology of CS and second how epithelial plasticity may play a role in the local and metastatic progression of this tumor type.

Potential Etiology of CS

CS is characterized by the presence of distinct epithelial and mesenchymal components. These subsets of epithelial and mesenchymal cells are hypothesized to arise in one of three ways as follows (McCluggage, 2002b):

1. The carcinomatous and sarcomatous compartments arise independently from distinct tumors (the collision theory);

2. Both components are derived from a single, transformed progenitor cell that diverges into epithelial-like and mesenchymal-like phenotypes (the combination theory); and/or

3. The sarcomatous component evolves from epithelial components via phenotypic plasticity (the conversion theory).

4. The carcinomatous component evolves from the mesenchymal components via phenotypic plasticity (this

less invoked conversion theory is not considered possible by many, but is presented here for completeness and as a testament to how little we actually know about the biology of these tumors).

Contrary to the collision theory, there are numerous examples in which both the epithelial-like and mesenchymal-like cells within CS can be traced to a clonal origin. Early studies using PCR of the HPRT gene in various tissues suggested a monoclonal derivation for CS (Millis et al., 1994; Thompson et al., 1996). In one investigation, the authors analyzed distinct populations of epithelial and mesenchymal cells from mammary CS tumors that were separated by microdissection (Zhuang et al., 1997). The authors noted that while common mutations were present in both carcinomatous and sarcomatous phenotypes, loss of heterozygosity was found only in the mesenchymal cells. Based on these observations, the authors postulated that the sarcomatous component arose from subsequent mutation of the primary carcinoma (Zhuang et al., 1997). Similarly, loss of heterozygosity analysis in esophageal CS using 25 microsatellite markers on multiple chromosomal arms suggested that a squamous cell carcinoma gave rise to a CS-like tumor (Matsumoto et al., 2004). Conversely, the authors could not find support for a sarcomatous component giving rise to a carcinoma (Matsumoto et al., 2004). In a case report of hepatic CS, array comparative genomic hybridization (aCGH) identified a common +6p in both carcinomatous and sarcomatous phenotypes (Schaefer et al., 2012). Ten mutations were observed in the carcinomatous region, with three mutations in the sarcomatous element (Schaefer et al., 2012). Based on these observations, the authors postulate that this tumor arose from a hepatocellular carcinoma stem-like cell that subsequently diverged into a sarcomatous phenotype and an undifferentiated carcinoma that underwent additional genomic mutation (Schaefer et al., 2012). Together, these studies rule out the collision theory and suggest that either the combination theory or conversion theory is responsible for the development of biphasic phenotypes within CS. Yet, despite the fact that most CS cases appear to be monoclonal in origin, there are also rare cases in which the collision of two independent neoplasms may play a role (McCluggage, 2002b; Jin et al., 2003). Interestingly, in these cases, McCluggage (2002b) points out that collision tumors may have better prognosis than monoclonally-derived CS (McCluggage, 2002b). Aside from these rare instances, the vast majority of CS cases appear to represent cancers of monoclonal origin, most likely originating from an epithelial-like cell type. Indeed, it is noteworthy that patients diagnosed with sarcomatoid carcinoma of the prostate typically have a history of adenocarcinoma and undergo brachytherapy, radiation therapy, or hormone therapy. A previous history of adenocarcinoma suggests that, at least in the prostate, CS may represent recurrent primary adenocarcinomas that have undergone EMT. Consistent with the hypothesis that sarcomatous

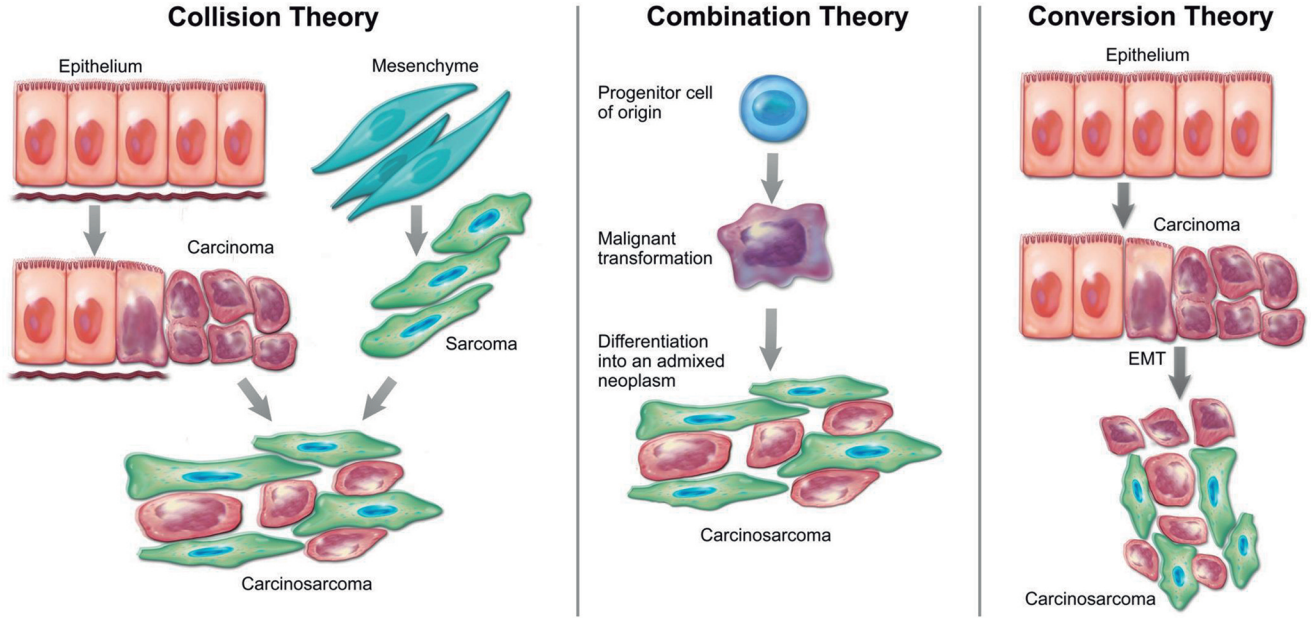

Fig. 2. Theories for the etiology of CS. Based on the collision theory, CS arises from two distinct neoplasms, one a carcinoma and the other a sarcoma. In the combination theory, CS is hypothesized to be derived from a transformed progenitor cell of origin, which subsequently differentiates into carcinomatous and sarcomatous components. The conversion theory posits that a carcinoma undergoes an epithelial-mesenchymal transition (EMT), leading to an admixed cancer comprised of both epitheliod and spindle-like cells. The other possibility, mesenchymal-epithelial transition (MET) from a sarcomatous neoplasm has not been included because it has not been observed clinically. Nonetheless, we hold it as hypothetically possible.

elements are derived from carcinomatous components, analysis of uterine CS mutations by deep sequencing revealed that significantly more genes were mutated in the sarcomatous elements than the carcinomatous component (Drs. Cheng-Han Lee and Melissa McConechy, University of British Columbia, personal communication). Below, we discuss the evidence that implicates EMT pathways in the pathogenesis and/or progression of CS.

Immunohistochemical evidence for epithelial plasticity in CS

IHC analyses of patient specimens have provided insights regarding the potential role of EMT in CS. For example, a survey of 12 cases of uterine CS revealed the presence of focal keratin and MUC1 (epithelial membrane antigen) staining within the spindle cell component and focal vimentin within epithelial cells (Bitterman et al., 1990). These results indicate that cells appearing to be histologically mesenchymal-like express epithelial biomarkers while cells appearing to be histologically epithelial-like express mesenchymal biomarkers. It is possible that these cells, which display morphological characteristics discordant with their biomarker expression, represent cells in transition between phenotypic states. Similar findings were also reported in a set of 31 malignant mixed Müllerian tumors, with keratin positivity in the stromal component of 48% of cases and vimentin positivity in the epithelial component of 35% of cases (Meis and Lawrence, 1990). A later case report of a patient with pulmonary CS also revealed expression of MUC1 in both carcinomatous and sarcomatous components (Haraguchi et al., 1999). Some of the sarcomatous-like cells also had desmosomal connections, which are characteristic of epithelial cells (Haraguchi et al., 1999). Immunohistochemical staining of primary cutaneous CS found co-expression of EpCAM and vimentin on the sarcomatoid-like cells (Paniz Mondolfi et al., 2013). Perhaps more interestingly, ultrastructural features were consistent with both epithelial and mesenchymal differentiation within the same cell (Paniz Mondolfi et al., 2013). Similarly, DeLong and colleagues found that the sarcomatoid components of sarcomatoid renal cell carcinomas expressed both cytokeratin AE1/AE3 and vimentin in 97% and 56% of cases, respectively (DeLong et al., 1993). Along similar lines, an analysis of pulmonary CS identified upregulation of the mesenchymal markers vimentin and fascin, along with expression of nuclear c-Jun. The authors postulated that c-Jun may be responsible for the EMT-like phenotype of the sarcomatous components (Blaukovitsch et al., 2006). Indeed, the authors point out, c-Jun has been linked to expression of vimentin in preclinical studies using cell lines (Wu et al., 2003). IHC of EMT markers in endometrial CS revealed distinct expression of E-cadherin only in the epithelial component, but expression of mesenchymal markers vimentin and N-cadherin in both the epithelial and mesenchymal cells (Castilla et al., 2011). Taken together, these studies suggest that CS, although made up of morphologically distinct epithelial and stromal elements, can also harbor transitional cells that co-express both epithelial and mesenchymal biomarkers and possess ultrastructural features of both epithelial and stromal cells. Despite these intriguing observations, it remains to be seen whether these transitional cells are found in all CS tumors.

Of particular note, the relative amounts of epithelial-like and stromal-like cells within CS tumors may have some prognostic value. For example, a clinico-pathological analysis of malignant mixed Müllerian tumors indicated that patients whose tumors were more sarcomatous in nature had shorter recurrence-free survival than those with larger epithelial-like compartments (Menon et al., 2013). In addition, Amant et al. (2002) suggested that CS may transition from a predominating epithelial tumor to a more sarcomatous tumor type during progression (Amant et al., 2002). The apparent progression from a less aggressive, epithelial-dominated tumor to a more aggressive, sarcomatous tumor mirrors the prognostic significance of EMT biomarkers in carcinoma progression. Indeed, multiple studies have shown that EMT biomarkers are prognostic for poorer survival in patients with squamous cell carcinoma (Hasan et al., 2013), breast cancer (Karihtala et al., 2013; Yamashita et al., 2013), prostate adenocarcinoma (Behnsawy et al., 2013), lung carcinoma (Reka et al., 2014), colorectal carcinoma (Kahlert et al., 2011; Lee et al., 2013; Toiyama et al., 2013), and numerous other cancers (Gasparotto et al., 2011; Harada et al., 2012; Fang et al., 2013; Yamada et al., 2013; Gu and Choi, 2014).

Molecular analyses of epithelial plasticity in CS

There are few molecular investigations related to the role of epithelial plasticity in CS; however, the available data suggest that parallels exist between the EMT factors involved in carcinoma progression and those at play in CS development. For example, Gregory et al. (2008) reported a loss of E-cadherin and downregulation of the miR200 family in sarcomatoid metaplastic breast cancers compared to invasive ductal carcinomas. The miR200 family of microRNAs is important for maintenance of an epithelial phenotype (Gregory et al., 2008). These microRNAs act by repressing the mesenchymal transcription factors, ZEB1 and ZEB2 (Gregory et al., 2008). Similarly, Castilla et al. (2011) found downregulation of the miR200b-200a-429 cluster and the miR200c-141 cluster within the mesenchymal-like cells compared to epithelial cells of endometrial CS. The authors also found upregulation of ZEB1 and ZEB2 within the mesenchymal-like CS cells. The EMT transcription factors Snail, Twist1, and TCF4 were also upregulated in the mesenchymal-like compartment compared to the epithelial portions of the tumors. In a

more comprehensive analysis, Chiyoda et al. compared the gene expression profiles of 14 endometrial CS, 24 endometrial carcinomas, and 8 uterine sarcomas. Interestingly, hierarchical clustering of gene expression data placed CS in the same cluster as sarcomas, while carcinomas formed a unique clade (Chiyoda et al., 2012). Additionally, CS and sarcomas were distinguished from carcinomas by expression of genes involved in EMT, including Zeb1, Twist, Snail, and members of the TGF-β signaling pathways (Chiyoda et al., 2012). Using an independent group of CS samples, the authors showed that the targets of TGF-β, Smad2/3, were significantly more phosphorylated in both the carcinomatous and sarcomatous components of CS compared to carcinomas (Chiyoda et al., 2012). The authors also showed gain of chromosomal regions corresponding to the *TGFB1* locus in 4/7 CS samples (Chiyoda et al., 2012). A similar comparison between endometrial CS and carcinomas identified a mesenchymal-like biomarker profile in CS compared to carcinoma (Diaz-Martin et al., 2014). Members of the miR200 family, along with the stemness-inhibiting miR203, were downregulated in CS compared to carcinomas (Diaz-Martin et al., 2014). These changes were also related to increased promoter methylation of the miR200 family and the E-cadherin promoter in CS samples (Diaz-Martin et al., 2014). The expression of miR200c and miR141 correlated strongly with the level of promoter methylation at this locus, and the methylation status at the miR141-miR200c locus correctly segregated the CS samples from the carcinomas (Diaz-Martin et al., 2014). These studies indicate that a number of the regulatory networks observed in EMT during carcinoma progression may also be active in the sarcomatoid-like component of CS.

The mutational landscape of CS is linked to EMT drivers

As is the case with much of CS biology, the mutational landscape of CS remains poorly characterized. Early studies found mutations within TP53 in sarcomatoid renal cell carcinoma (Oda et al., 1995), prostate CS (Sak et al., 1997; Delahunt et al., 1999), and CS of the female genital tract (Costa et al., 1994). A subsequent study identified mutations in TP53, PIK3CA, KRAS, CTNNB1, and NRAS in 25%, 19%, 15%, 4%, and 2% of uterine CS tumors, respectively (Growdon et al., 2011). More recent investigations using targeted deep sequencing and other approaches are now casting additional light on the potential driver mutations

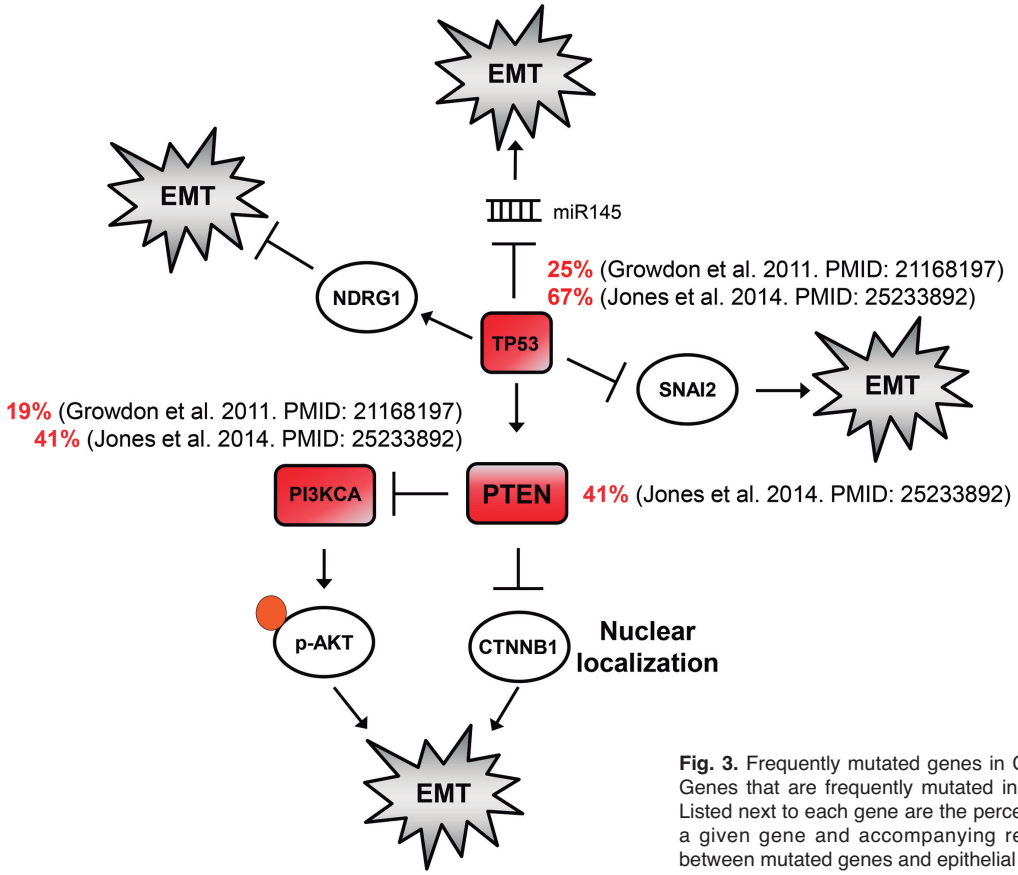

Fig. 3. Frequently mutated genes in CS are drivers of epithelial plasticity. Genes that are frequently mutated in CS are indicated in shades of red. Listed next to each gene are the percentage of CS cases with mutations in a given gene and accompanying references. Functional connections between mutated genes and epithelial plasticity are also indicated.

involved in CS. Analysis of 25 known cancer genes in 30 uterine CS found that the mutation profile of uterine CS clusters tumors into two types: an endometrioid, carcinoma-like mutation profile comprised of PTEN, ARID1A, PIK3R1, and POLE mutations and a serous-type carcinoma-like profile consisting of TP53, PPP2R1A, EP300, and FBXW7 mutations (Drs. Cheng-Han Lee and Melissa McConechy, University of British Columbia, personal communication). Interestingly, 60% of CS tumors harbored gene mutations involved in the PI3K pathway (Drs. Cheng-Han Lee and Melissa McConechy, University of British Columbia, personal communication). Whole exome sequencing of 22 uterine CS tumors also showed mutations in PI3K pathway genes in 59% of tumors (13/22), and TP53 mutations in 67% of tumors (Jones et al., 2014). These analyses further identified frequent mutations in chromatin remodeling genes ARID1A and ARID1B, suggesting that loss of this complex may be involved in the development of uterine CS (Jones et al., 2014).

Interestingly, some of the mutations observed in CS are mechanistically linked to epithelial plasticity. For example, while TP53 is classically known for its roles in cell cycle arrest and apoptosis (Kirsch and Kastan, 1998), multiple investigations have also shown that mutations in TP53 induce EMT (Engelmann and Putzer, 2014). Similarly, PTEN loss induces EMT in colorectal cancer cells (Bowen et al., 2009) and in mouse models of prostate cancer (Mulholland et al., 2012). Moreover, activation of the PI3K pathway through TGF-β, Ras, or WNT/β-catenin signaling drives EMT (Larue and Bellacosa, 2005; Mulholland et al., 2012) (Fig. 3). Frequent mutations within CS tumors in genes or pathways associated with EMT suggests that some functional connection may exist between these mutations and the development of an aggressive, EMT-like phenotype in CS.

Relationship between biphasic differentiation and stemness

The immunohistochemical and molecular analyses described above support the conversion theory; the hypothesis that CS develops from an epithelial-like primary tumor in which a subset of cells undergo EMT, thus giving rise to a biphasic tumor. In addition to upregulation and mutation of EMT pathways in CS development, several studies have also indicated that cancer stem cells may contribute to the plasticity observed in CS. For example, evaluation of breast CS tumors revealed that most of the CS tumors exhibited a basal-like phenotype (Sarrio et al., 2008). Similarly, the majority of the mesenchymal-like, invasive breast carcinomas were also classified as basal-like, which has been shown to be enriched in stem-like cells (Sheridan et al., 2006). The authors postulated that cancers with a basal-like, stem cell phenotype have a higher potential to undergo EMT (Sarrio et al., 2008). In another investigation, Castilla et al. noted downregulation of miR203 in endometrial CS (Castilla et al., 2011), which is an inhibitor of stemness (Lena et al., 2008; Yi et al., 2008; Wellner et al., 2009; Taube et al., 2013). Based on this, the authors propose that a connection may exist between the EMT and stemness phenotypes in endometrial CS. Indeed, multiple investigations have pointed to a link between the EMT phenotype and stemness (Mani et al., 2008; Wellner et al., 2009; Tellez et al., 2011; Zhou et al., 2014). While these analyses highlight the connection between stemness and phenotypic plasticity, it is unclear whether the propensity for CS tumors to be enriched in stem-like cells is a cause or consequence of CS development.

Epithelial plasticity in CS metastasis

While epithelial plasticity appears to contribute to the biphasic nature of CS tumors, it is unclear whether plasticity is causally linked in any way to CS metastasis. The few case reports that have described CS metastases vary in their results. Some have found that the metastases often exhibit sarcomatoid-like features (Takeyoshi et al., 2000; Dyke et al., 2014; Kiuru et al., 2014) while others have reported metastasis of mixed histology (Haddad and Reyes, 1970) or only the carcinomatous component (Bitterman et al., 1990; Piura et al., 2009). Data from our group using xenograft mouse models suggests that mesenchymal-like cells from a human uterine CS cell line (CS-99) undergo MET upon metastatic colonization (Somarelli et al. unpublished observations). Interestingly, the CS-99 cells require MET to form macrometastatic colonies (Somarelli et al. unpublished observations). These observations suggest that mesenchymal-like CS-99 cells undergo a phenotypic switch to a more epithelial-like state during metastasis. Yet, this study did not address whether the epithelial-like or stromal-like components (or both) drive CS metastasis.

Unanswered questions

CS tumors are unique examples of epithelial plasticity, with elements comprised of both epithelial and stromal cells. The current literature suggests that sarcomatous components of CS may represent post-EMT-like events that derive from carcinomatous origin. Interestingly, many of the same master regulators implicated in EMT of carcinomas have been observed in CS, and several of the most frequent mutations identified in CS samples are linked to EMT pathways. In addition, CS tumors appear to possess a stem-like phenotype, which may contribute to the plasticity inherent to these neoplasms. Along these lines, some investigations have described the presence of epithelial cells with mesenchymal biomarkers/structural features and vice versa within CS tumors, which supports the conversion theory of CS etiology. Despite these observations, numerous unanswered questions remain, including:

1. Do the sarcomatous components truly derive from

an epithelial cell of origin via EMT (i.e. via conversion theory)? If so, is this EMT reversible?

2. What is the relationship, if any, between the relative amounts of epithelial and mesenchymal cells within a patient's tumor and chemoresistance, radioresistance, and/or surgical recurrence?

3. Which of the constituents of CS metastasize? Do both components (epithelial and stromal) contribute to the metastatic cascade?

4. Are there common molecular lesions (mutations/translocations, epigenetic events) causally related to CS development in different organs (prostate, breast, kidney, uterus, etc). that suggest a cell of origin and, more importantly, therapies that may be directed at these targets to prevent/delay metastatic spread?

Preclinical investigations using xenograft models and lineage tracing systems may shed light on many of these unanswered questions. In addition, the expansion of circulating tumor cell biology into the study of CS may hold promise for uncovering which phenotype, epithelial and/or mesenchymal, is the driving force behind metastatic disease. Whatever the methodology might be, a more complete understanding of the biology of CS metastasis will hopefully elucidate actionable targets and pathways to treat these highly aggressive neoplasms.

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