Cancer Stem Cells in Endometrial Cancer

Subjects: Oncology

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Endometrial cancer is one of most common types of gynaecological tumours in developing countries. It has been suggested that cancer stem cells play an important role in the development of endometrial cancer. These are a subset of highly tumorigenic cells with similar features to normal stem cells (unlimited proliferation, multi-potential differentiation, self-renewal, aggressiveness, invasion, recurrence, and chemo- and endocrine therapy resistance). Wnt/β-catenin, Hedghog, and Notch1 are the most frequently activated pathways in endometrial cancer stem cells. The presence of cancer stem cells is associated with the resistance to chemotherapy caused by different mechanisms.

Keywords: cancer stem cells ; endometrial cancer ; CD133 ; CD117 ; CD44

1. CD133

CD133 is a pentaspan transmembrane glycoprotein, the sub-cellular localisation of which enables its interaction with lipid rafts participating in the signalling cascade [1]. Mizrak et al. [2] suggested that this molecule could be involved in cell membrane organisation. Jaksch et al. [3] showed that the expression of CD133 in both CSCs and normal cells depended on the cell cycle. Various studies indicated that CSCs expressing CD133 comprised 5.7–27.4% of cells in primary endometrial tumours and their presence was associated with a worse prognosis [4]. The high expression of CD133 on the surface of CSCs correlates with a greater self-renewal ability, higher proliferative potential, lymphovascular invasion, and a poor prognosis [1][5]. Rutella et al. [4] demonstrated in a mouse model that cells expressing CD133 showed an increased ability to aggressively proliferate and form colonies compared with CD133-negative cells [4]. Moreover, CD133-positive cells had a greater ability to migrate from the primary mass to blood vessels and other organs and a higher resistance to chemotherapy than CD133-negative cells. Rutella et al. [4] suggested that CD133-positive populations of endometrial cancer cell lines form floating spheres and colonies that originate from clonal proliferation. Additionally, Kyo et al. [6] provided evidence that CD133-positive cells have a higher colony-forming ability in vitro and enhanced tumorigenicity in immunocompromised mice. A high CD133 expression in specimens of endometrioid-type endometrial cancer was associated with decreased overall survival compared with a low CD133 expression [6]. In addition to the CD133 expression, the FIGO stage and histological grade negatively influenced overall survival rates. The CD133 expression (hazard ratio (HR) 3.90; $p < 0.045$) and FIGO stage (HR 3.94; $p < 0.042$) were independent predictive factors for patient survival [6]. The expression of CD133 translates into higher rates of endometrial tumour relapse and worse survival [4][7][8]. A high expression of TGFB1 has been observed in the CD133-positive CSC subpopulation of endometrial cancer cells. TGF-β1 was found to activate EMT to trigger metastasis [4]. The TGF-β1/CD133 pathway was found to stimulate cell invasion, stem-like characteristics, and therapy resistance [9]. Moreover, TGF-β1 can stimulate genomic instability via hindering the repair of DNA double-strand breaks [10][11]. Nakamura et al. [12] suggested that CD133 was a risk factor for endometrial cancer due to the higher proliferative and tumorigenic potential and cisplatin and paclitaxel resistance. The results of another study revealed that CD33-positive cells have increased tumorigenic potential [13]. Aggressive tumour behaviour has also been linked with the upregulation of ABCG2 and matrix metalloproteinases (MMPs) in CD133-positive cells [6]. The expression of MMP14 (which encodes MT1-MMP) increases the invasive capacity of CD133-positive cells, whereas the knockdown of MMP14 with small interfering RNA (siRNA) mostly abolishes this effect.

The expression of CD133 in endometrial CSCs was found to be frequently accompanied by the upregulation of CD44 and NES, which enhanced proliferation and infiltration [4][14][15]. Bokhari et al. [16] confirmed that NES knockdown hindered cell growth and limited the invasive potential and colony formation abilities of endometrial cancer cell lines, whereas its overexpression was associated with a malignant phenotype.

2. CD44

CD44 is a transmembrane adhesion molecule suggested to be a useful marker of CSCs in endometrial cancer. This molecule is also involved in cancer invasion and metastasis [8][13]. CD44 expression was found to positively correlate with

PDL1 expression in various tumours, as well as with immune infiltration [17]. This adhesion molecule has been demonstrated to be involved in tumour cell invasion and metastasis in endometrial cancer cell lines [8]. Zagorianakou et al. [18] linked CD44 expression with an enhanced proliferation of endometrial carcinomas of the endometrioid type, a higher tumour grade, and progesterone receptor status. Park et al. [14] found a close relationship between CD133 or CD44 expression and endometrial cancer progression and a poor prognosis.

3. SMOC2

Lu et al. [19] suggested that SPARC-related modular calcium binding 2 (SMOC2) could also be used as a signature gene of endometrial CSCs. SMOC2 protein, the levels of which are enhanced during embryogenesis and wound healing, shows angiogenic activity and is capable of stimulating endothelial cell proliferation and migration [19][20][21]. Lu et al. [19] found that SMOC2 expression was increased in sphere cultures and in CD133/CD44-positive cells compared with CD133/CD44-negative cells and also boosted the chemoresistance of endometrial cancer cells. Furthermore, SMOC2 silencing resulted in the diminished clonogenic potential of endometrial cancer and reduced the expression of stemness-related genes, including SOX2, OCT4, and NANOG [19]. In endometrial cancer, the SMOC2-related activation of WNT/β-catenin signalling promoted the progression of endometrial cancer since this pathway is vital for cell growth, differentiation, proliferation, and survival [19][22][23]. Furthermore, this pathway is involved in the formation and maintenance of stem cells and CSCs [22].

4. CXCR4

The invasive and metastatic phenotypes of CSCs have also been suggested to be mediated by the chemokine ligand/receptor axis [6]. In endometrial cancer, CXC motif chemokine receptor 4 (CXCR4) was demonstrated to be highly expressed by some tumour cells [24]. The activation of CXCR4, a stromal cell-derived factor-1 receptor, triggers signalling pathways promoting increased survival, enhanced proliferation, the degradation of the extracellular matrix, drug resistance, and angiogenesis in malignant tumour cells [25]. The expression of both CXCR4 and CD133 has been reported in all types of human tumours, including endometrial cancer [15]. Moreover, CXCR4 was found to be upregulated considerably in endometrial tumours compared with atypical, simple hyperplasia and normal endometrial tissue [13]. The results of several studies have found that the CXCL12/CXCR4 axis is partly responsible for tumour progression, angiogenesis, metastasis, and survival [26]. The actions of CXCR4 are associated with the induction of signalling pathways involved in gene transcription, survival, proliferation, and chemotaxis. Sun et al. [15] demonstrated that CD133/CXCR4-positive endometrial cancer cells comprised less than 10% of the total population, which is in agreement with the findings that CSCs constitute only a small percentage of cells in malignant tumours. Cioffi et al. [27] demonstrated considerably lower two-year survival rates in patients with a high expression of CD133 and CXCR4 compared with patients with a low CD133 and CXCR4 expression. The growth of CD133/CXCR4-positive cells in vitro was greater than that of CD133/CXCR4-negative cells, indicating enhanced proliferative properties. Sun et al. [15] also revealed that CD133/CXCR4-positive cells have an increased potential to form more spheres and colonies, which appear to be typical characteristics of stemness in various tumours [28][29]. CD133/CXCR4-positive cells also exhibited a higher expression of stemness genes [15]. The injection of CD133CXCR4-positive cells into nude mice was associated with tumour formation, and tumour formation was not observed following inoculation with CD133/CXCR4-negative cells [15].

5. CD117

CD117 (c-kit) is a cell surface receptor tyrosine kinase that has been proposed as a CSC marker in various tumour types [30][31]. Following stimulation by stem cell factor, CD117 triggers cell replication, differentiation, and survival, and CSCs acquire stemness properties [32][33][34]. The results of some studies have demonstrated that endometrial CSCs expressing CD117 have increased the proliferative and colony-forming potential [30][35]. Zhang et al. [35] suggested that a high CD117 expression could be used as an independent prognostic factor. In addition to endometrial cancer, the expression of CD117 in CSCs has also been demonstrated in ovarian and lung cancer [33][36].

6. CD55

CD55 is an intrinsic cell surface complement inhibitor [31]. A high expression of CD55 has been reported in endometrial cancer cells and CSCs. Cells expressing this inhibitor displayed a higher self-renewal ability, as well as a higher resistance to chemotherapy, than CD55-negative cells [37]. CD55 expression in endometrioid ovarian and endometrial CSCs was demonstrated to enhance self-renewal properties and cisplatin resistance. In endometrial endometrioid cell lines, the inhibition of CD55 with saracatinib was associated with cisplatin resensitisation [37].

7. ALDH1

ALDH1 was demonstrated to be highly active during the early steps of stem cell differentiation [38][39]. Endometrial cancer cells with a high ALDH1 expression were found to be more tumorigenic and invasive, as well as resistant to cisplatin therapy and associated with a worse prognosis in patients with endometrial cancer (p = 0.01 for overall survival), compared with cells with a low expression of ALDH1. Additionally, Rahadiani et al. [40] observed that cells with a higher ALDH1 expression had higher tumorigenic potential, as well as increased invasiveness and resistance to cisplatin, compared with cells with a low ALDH1 expression. These features were associated with a poor prognosis in patients with endometrial cancer [40]. The expression of ALDH and CD133 in debulked primary tumour specimens was found to correlate with poor patient survival [38]. Mori at al. [41] observed that ALDH-dependent glycolytic activation mediated stemness and chemoresistance in spheroid uterine endometrial cancer derived from patients. The disulfiram and N,N-diethylaminobenzaldehyde (DEAB)-related inhibition of ALDH1 decreased the proliferation of spheroid CSCs [42]. Ran et al. [43] suggested that the ALDH expression in endometrial CSCs mediates autophagy, which contributes to CSC survival and chemoresistance, since they observed a decrease in cell growth and self-renewal potential following the use of an autophagy inhibitor (3-methyladenine or chloroquine).

8. NANOG

NANOG expression was suggested to be useful as a diagnostic marker, enabling the differentiation between true dysplasia and reactive lesions [5][44]. An increased expression of NANOG has been detected in precancerous lesions (high-grade dysplasia), as well as in cancerous tissue. In endometrial CSCs, NANOG expression was found to be regulated by transcription factor 3 (TCF3), OCT4, and SOX2 [30]. Grubelnik et al. [45] suggested that the high expression of NANOG is associated with a more advanced cancer, a higher cancer grade, resistance to treatment, and, thus, a worse prognosis. NANOG has also been suggested to be involved in the acquisition of stem-cell-like features, including self-renewal and immortality [5]. Al-Kaabi et al. [5] demonstrated the expression of NANOG in 88.37% of endometrial carcinoma cases. Moreover, they reported that NANOG expression correlated with deep myometrial invasion, a higher cancer grade, and a positive lymph node status, all of which indicated a worse prognosis. According to other studies, a high NANOG expression translates into the presence of poorly differentiated, advanced tumours and poor patient survival [46][47][48].

9. Other

Endometrial CSCs have also been reported to express the neuroendocrine marker synaptophysin [49]. Helweg et al. [49] observed that nuclear synaptophysin, CD133, CD44, and Nestin indicated endometrial-CSC-like characteristics. Additionally, the levels of CK-18, a structural protein normally present in many single-layer epithelia, were demonstrated to correlate with the clinical stage, number of positive lymph nodes, metastasis, and recurrence, as well as poorer overall and disease-free survival [50].

The utility of the aforementioned markers has been suggested in many studies; however, Tabuchi et al. [51] demonstrated that CSC populations in uterine endometrioid adenocarcinoma showed functional heterogeneity and suggested that there was no distinctive biomarker for the identification of CSCs as various colonies within the same tumour could express different markers. Spherical clones were found to be less tumorigenic but more resistant to chemotherapy. In turn, leukaemia-like clones show opposing features. Therefore, more studies are required to understand the functional mechanisms of CSCs and to target these cells in order to improve the effectiveness of cancer treatment and prevent its recurrence.

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