
PDGF-α and PDGF-β are expressed in endometrial stromal sarcoma: a potential therapeutic target for tyrosine kinase inhibitors?

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Sir: Endometrial stromal sarcomas (ESS) are rare mesenchymal, well-vascularized, hormone-sensitive tumours occurring in premenopausal women. Treatment of ESS is primarily surgical, but recurrence rates are high, despite adjuvant chemo-, radiotherapy and hormonal therapy. Little is known about the aetiology or the genetic mechanisms involved in the oncogenesis of ESS. ESS lack genetic mutations of c-KIT and are thought unlikely to respond to treatment with tyrosine kinase inhibitors, e.g. imatinib mesylate. Possible antiproliferative activities of tyrosine kinase inhibitors include inhibition of class III receptor tyrosine kinase members such as c-KIT, platelet-derived growth factor (PDGF) receptor-α and -β. Activation of tyrosine kinase receptors in the absence of receptor mutations can occur via auto- and paracrine stimulation loops through PDGF-α and PDGF-β.

In the present study, we evaluated the immunohistochemical expression of PDGF-α (CD140α, clone E10; 1:1000 dilution), PDGF-β (CD140β, clone H55; 1:100 dilution; both from Santa Cruz Biotech, Santa Cruz, CA, USA) and c-KIT protein (CD117, clone 104D2; 1:8 dilution; Dako, Glostrup, Denmark) in 37 ESS. Immunoreactivity was scored as negative (< 10% positive tumour cells), weakly positive (10–50% positive cells) and strongly positive (> 50% positive tumour cells). All ESS were negative for c-KIT. PDGF-α was strongly expressed in tumour cells and endothelial cells of 17/37 ESS in a cytoplasmic and membran-
**Table 1. Summary of staining results in endometrial stromal sarcomas**

<table>
<thead>
<tr>
<th>Staining pattern</th>
<th>PDGF-α (CD140α)</th>
<th>PDGF-β (CD140β)</th>
<th>c-KIT (CD117)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly positive*</td>
<td>17/37</td>
<td>4/37</td>
<td>0/37</td>
</tr>
<tr>
<td>Weakly positive†</td>
<td>5/37</td>
<td>4/37</td>
<td>0/37</td>
</tr>
<tr>
<td>Negative‡</td>
<td>13/37</td>
<td>29/37</td>
<td>37/37§</td>
</tr>
</tbody>
</table>

*Strongly positive: > 50% of tumour cells showed a cytoplasmic and membranous staining profile.
†Weakly positive: between 10% and 50% positive tumour cells showed a cytoplasmic and membranous staining profile.
‡Negative: 0–10% of tumour cells showed a cytoplasmic and membranous staining profile.
§Negative: in four cases, single cells stained positive for c-KIT.

ous pattern (Figure 1a,b). Weak immunoreactivity was identified in 5/37 ESS. PDGF-β showed predominantly weak staining in 4/37 ESS (Figure 1c, see Table 1).

The membranous staining pattern results from binding of PDGF to its receptor and serves as indirect proof of receptor up-regulation. In the absence of activating receptor mutations, PDGF may be involved in up-regulation of tyrosine kinase receptors via alternative mechanisms, e.g. autocrine or paracrine stimulation loops, loss of phosphatase activity, cross-activation by another kinase or promoter activation via methylation. PDGF and PDGF receptors are expressed abundantly in tumour stroma and vasculature and play important roles in angiogenesis and inhibition of apoptosis. Several studies have suggested that PDGF might affect endothelial cell growth directly. PDGF-β receptors are involved in pericyte recruitment to capillaries and development of smooth muscle cells in vessels and tyrosine kinase inhibitors have been shown to decrease microvessel density in ovarian carcinoma. Tyrosine kinase inhibitors are well-tolerated treatment options for patients with metastasizing gastrointestinal stromal tumours. Our observations suggest that a subset of patients with ESS may benefit from treatment with tyrosine kinase inhibitors. Imatinib mesylate has been tried in women with ESS on empirical grounds with good results (personal unpublished observation from a survey of the Endometrial Stromal Sarcoma Health Group, an internet group for women with ESS, www.GlobalHealthNetwork.org, see also 3). In particular, patients with recurrent or metastasizing ESS, who do not tolerate adjuvant hormonal treatment such as aromatase inhibitors, due to severe side-effects, or patients who relapse on other therapy regimens, may be candidates for a clinical trial of tyrosine kinase inhibitor therapy.

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B Liegl
O Reich¹
F F Nogales²
S Regauer

Institute of Pathology and ¹Department of Obstetrics and Gynaecology, Medical University Graz, Austria, and ²Department of Pathology, University of Granada, Granada, Spain


**Florid cystic endosalpingiosis of the uterus**

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Sir: We describe a case of florid cystic endosalpingiosis in a 49-year-old woman. A total abdominal hysterectomy and bilateral salpingo-oophorectomy specimen removed for benign disease showed numerous cystic structures on the surface of the uterus and both ovaries. Histological examination showed cysts lined by benign columnar ciliated (tubal type) epithelium with foci of psammomatous calcification. This morphology and the supportive immunohistochemistry established the diagnosis of florid cystic endosalpingiosis.