**Introduction**

Malignant pleural mesothelioma (MPM) is a highly aggressive, incurable, chemoresistant tumour. Recent studies have shown that Mesenchymal stem cells (MSC) can home to and incorporate into the tumour stroma. Their tumour tropism can be used to deliver Tumour necrosis factor related apoptosis inducing ligand (TRAIL), a transmembrane protein that selectively induces apoptosis in transformed cells. However, not all tumours are sensitive to TRAIL. TRAIL works through triggering the extrinsic apoptotic pathway while conventional chemotherapeutic agents act by triggering the intrinsic apoptotic pathway. We hypothesised the crosstalk between these two pathways could be exploited by combining chemotherapy and MSC-TRAIL in MPM tumour cell lines.

**Methods**

MSC were engineered to express TRAIL using a lentiviral plasmid vector. A Tetacycline (Tet)-inducible system was used as a backbone to control the expression of TRAIL. Apoptosis induced by recombinant TRAIL, MSC-TRAIL in MPM cell lines on combination with Vorinostat, a chemotherapeutic agent, was measured by Annexin-V/DAPI based flow cytometry.

**Results**

The combination of recombinant TRAIL and Vorinostat act synergistically to induce apoptosis in MPM cell lines. Recombinant TRAIL and Vorinostat, as monotherapies induce 7.17% and 51.35% apoptosis in an MPM cell line JU77 respectively. In CRL2081 and ONE58 cell lines, recombinant TRAIL induces 56.75% and 13.41% apoptosis while Vorinostat leads to 78.95% and 43.97% apoptosis respectively. The combination of recombinant TRAIL and Vorinostat shows an increased amount of apoptosis in JU77, CRL2081 and ONE58 cell lines at 80.77%, 96.6% and 77.27% respectively (Table 1).

Similar synergistic effect was observed when TRAIL expressing MSCs were co-cultured with Vorinostat treated MPM cell lines. MSC-TRAIL induced apoptosis in JU77 (48.73%), CRL2081 (57.63%) and ONE58 (53.8%) cells. Combined treatment of Vorinostat and MSC-TRAIL significantly increased apoptosis to 77.7% in JU77, 90.93% in CRL2081 and 77.8% in ONE58 cells (Table 1).

**Conclusion**

The combination of Vorinostat and recombinant TRAIL acts synergistically to induce apoptosis in malignant pleural mesothelioma cells. Similar affect is observed with the combination of MSC-TRAIL and Vorinostat. This study indicates that Mesenchymal stem cells can be used as vectors for delivery of TRAIL and upon combination with Vorinostat, could be a potential therapy for malignant pleural mesothelioma.

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**Abstract S127 Table 1. Apoptosis induced by recombinant TRAIL and MSC-TRAIL on combination with Vorinostat**

<table>
<thead>
<tr>
<th></th>
<th>rTRAIL</th>
<th>Vorinostat</th>
<th>rTRAIL and Vorinostat</th>
<th>MSC-TRAIL not activated</th>
<th>MSC-TRAIL Activated</th>
<th>MSC-TRAIL not Activated + Vorinostat</th>
<th>MSC-TRAIL Activated + Vorinostat</th>
</tr>
</thead>
<tbody>
<tr>
<td>JU77</td>
<td>7.17%</td>
<td>51.35%</td>
<td>80.77%</td>
<td>10.32%</td>
<td>48.73%</td>
<td>47.44%</td>
<td>77.7%</td>
</tr>
<tr>
<td>CRL2081</td>
<td>56.75%</td>
<td>78.95%</td>
<td>96.6%</td>
<td>37.3%</td>
<td>57.63%</td>
<td>81.45%</td>
<td>90.93%</td>
</tr>
<tr>
<td>ONE58</td>
<td>13.41%</td>
<td>43.97%</td>
<td>79.27%</td>
<td>10.88%</td>
<td>53.8%</td>
<td>49.25%</td>
<td>77.8%</td>
</tr>
</tbody>
</table>

MPM cells are treated with recombinant TRAIL (100ng/ml) and Vorinostat (2.5μM). MSC are plated in 1:1 ratio with tumour cells. MSC are activated with doxycycline to induce TRAIL expression.
ROLE OF CADM1 IN SQUAMOUS CELL CARCINOMA PROGRESSION

S Vallath, EK Sage, VH Teixeira, SM Janes, A Giangreco; Lungs for Living, Div. of Medicine, UCL, London, UK
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Introduction Lung cancer is the second most common cancer in the UK with about 42,000 people being diagnosed in 2010 alone (Office of National Statistics, 2012). With a tendency to form invasive metastases coupled with its frequent late stage diagnosis, lung cancer attributes to the largest cause of cancer related mortality worldwide. Despite advances in treatment and care, the five-year mortality rate remains at 90%. There is a desperate need to improve patient survival, which can be achieved partly through improved screening techniques and more importantly by expanding our understanding of the molecular changes associated with lung cancer development and progression.

We investigate the role of a tumour suppressor gene, first identified in lung cancer, tumour suppressor in lung cancer 1 (TSLC1) or cell adhesion molecule 1 (Cadm1) in regulating squamous cell carcinoma (SqCC) growth and metastases.

Methods Cadm1 expression levels were examined using q-PCR analysis on human pre-invasive airway and normal lung tissue collected as part of an on-going UCL/CRUK longitudinal-tracking study (Lung-Surveillance and Lung-SEARCH trials). Cadm1 was introduced into an established SqCC cell line (A431) and in vitro functional assays performed to investigate its effect on tumour growth, progression and invasion. Pre-clinical mice models were used to study the effect of Cadm1 expression in tumour growth and metastatic potential.

Results q-PCR analyses demonstrated that loss of Cadm1 expression is a frequent early event in pre-invasive human airway compared to normal tissue (p = 0.001). Functional assays using A431, with Cadm1 reintroduced, showed Cadm1 expression levels directly associated with a significant decrease in cell proliferation (p = 0.001) over 10 days and significant reduction in invasion (p = 0.001) over 72 hours compared to control A431 cells without Cadm1. Pre-clinical xenograft tumourigenecity experiments in mice showed that Cadm1 expression significantly inhibited tumour growth (p = 0.01) together with a significant reduction in the number of metastases observed (p = 0.01) when compared with the control group.

Conclusion These data suggest that restoration of Cadm1 expression in human squamous cell carcinomas play an important role in regulation of tumour growth and metastasis. Understanding the mechanism through which Cadm1 expression is able to modulate cancer progression maybe therapeutically beneficial.