Nature Reviews Cancer | AOP, published online 12 October 2006; doi:10.1038/nrc2016

METASTASIS

A new player

DOI:
10.1038/nrc2016

URLs
ILEI (may be listed in Entrez as FAM3C)
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene&cmd=Retrieve&dopt=full_report&list_uids=10447

Using expression profiling to identify translationally regulated genes, Hartmut Beug and colleagues have identified a cytokine-like protein that seems to be a key player in metastatic progression.

Epithelial–mesenchymal transition (EMT) is involved in tumour metastasis, but the term encompasses a wide range of changes from a reversible scattering phenotype to a stable 'complete EMT'. The EpH4 mouse mammary epithelial cell line can undergo either scattering or complete EMT in response to different signalling pathways. Oncogenic Ras expressed in EpH4 cells (EpRas), in cooperation with transforming growth factor-β (TGFβ), causes EMT. Using Ras mutants that activate only specific downstream pathways, the authors previously determined that this EMT requires the activation of the ERK pathway (EpS35 cells), whereas the Ras-induced activation of the phosphatidylinositol 3-kinase pathway alone (EpC40 cells) induces scattering in response to TGFβ.

To identify the genes that are involved in complete EMT, the authors compared polysome-bound messenger RNA from cell pairs of EpRas, EpS35 and EpC40 cells that were either treated or not treated with TGFβ. They found that ILEI (interleukin-like EMT inducer), a member of a recently discovered family of proteins whose functions are largely unknown, is strongly upregulated at the translational level in the cells that were undergoing EMT, and these cells also secreted higher levels of ILEI. The expression of ILEI in EpH4 cells and their derivatives induced EMT in all cell types when grown in collagen gels, and recombinant ILEI protein was able to induce EMT in parent EpH4 cells.

The expression of ILEI in EpH4 cells, which are non-tumorigenic in mice, enabled tumour formation. ILEI increased tumour size in EpC40 cells, but did not seem to increase the proliferation of these cells, and the authors propose that local invasion in response to EMT might increase tumour growth. Tail vein injection experiments indicated that ILEI is also able to induce late steps in metastasis when expressed in EpH4 or EpC40 cells. Furthermore, the knockdown of *ILEI* using RNA interference prevented TGFβ-induced EMT in EpRas cells and reduced tumour formation and the inherent metastatic capacity of these cells *in vivo*.

So, is ILEI also expressed in metastatic human tumours? Because ILEI seems to be controlled translationally, the authors analysed protein expression. ILEI was not expressed in many epithelial tissues, but was seen in small dot-like structures (which could be storage vesicles) in secretory epithelia. However, many tumour types (breast, colon, prostate, lung, and head and neck) showed increased cytoplasmic expression of ILEI, which correlated with EMT at the invasion front (as analysed in human colon carcinomas). They further examined ILEI in samples from 43 patients with breast cancer with known outcome and found that the cytoplasmic expression of ILEI correlated with a significant decrease in metastasis-free and overall survival.

Beug and colleagues have identified ILEI as a clear player in EMT and metastasis in breast cancer, and possibly other cancers as well. Further studies of this cytokine are warranted to determine whether ILEI is a valid therapeutic target.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPER Waerner, T. *et al.* ILEI: a cytokine essential for EMT, tumour formation, and late events in metastasis in epithelial cells. *Cancer Cell* **10**, 227–239 (2006)