The role of AEG-1 in cervical cancer progression and response to therapy

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INTRODUCTION

- The epithelial-mesenchymal transition (EMT) converts epithelial cells into a mesenchymal phenotype, which is characterized by the loss of apical-basal polarity and cell-cell junctions, cytoskeleton remodelling and acquisition of migratory and invasive abilities.
- Having migrated to their target sites, mesenchymal cells may get their epithelial properties back through the reverse process termed mesenchymal-epithelial transition (MET).

CERVICAL CANCER

- Cervical cancer arises from the narrow end of the uterus and is the second most prevalent female cancer worldwide.
- Its progression is accurately described by the Federation of Gynecology and Obstetrics (FIGO) guidelines. Despite the generally good prognosis at early stages, many patients are still being diagnosed at advanced stages (l1–l4) where the mortality increases as a result of metastasis and recurrence (Fig. 2).
- Clapatin (Platinol®) and paclitaxel (Taxol®) constitute first-line clinical chemotherapy in metastatic or recurrent cervical cancer. However, drug resistance limits the curative effect in some cases although the molecular mechanisms are not fully understood.

AIMS

- By reviewing the current literature of EMT in the development of cervical cancer, this study aims to:
  - Investigate the role of AEG-1 in tumour progression and response to therapy
  - Evaluate the suitability of AEG-1 as a potential biomarker for cervical cancer monitoring and as a target for new drug development

RESULTS AND DISCUSSION

1. AEG-1 ACTS ON A PLETHORA OF SIGNALING PATHWAYS

A wealth of evidence implicates AEG-1 in several signalling pathways (Fig. 1), namely:
- Ha-Ras/Pi3K/Akt
- MAPK
- NF-κB
- Wnt/β-catenin

2. AEG-1 EXPRESSION IN CERVICAL CANCER AND CORRELATION WITH CLINICOPATHOLOGICAL FEATURES

AEG-1 is overexpressed in cervical cancer cell lines and human tumour samples within the cell membrane and cytoplasm, and significantly correlates with:
- FIGO staging
- Lymph node metastasis
- Overall survival (Fig. 2)

3. AEG-1 AND EMT

- CC020 activates AEG-1 via MAPK (ERK1/2) and Akt signaling pathways and increases the expression of mesenchymal markers vimentin, N-cadherin, and MMP2 (Fig. 3) in cervical cancer cells in vitro.

4. AEG-1 IN TUMOUR PROGRESSION AND METASTASIS

- AEG-1 silencing in cervical cancer cells in vitro results in:
  - Reduced proliferation (Fig. 4) and increased apoptosis
  - Reduced migration and invasion (Fig. 5)
  - Reduced angiogenesis

AEG-1 favours stem cell-like properties and promotes tumour progression and metastasis

5. AEG-1 AND RESPONSE TO THERAPY

- AEG-1 promotes resistance to clapatin and paclitaxel in cervical cancer cells in vitro (Fig. 6)
- AEG-1 induces:
  - Protective autophagy by upregulating LC3
  - Resistance to apoptosis by activating MAPK and NF-κB, thereby inhibiting the cleavage of caspase-3

AEG-1 has been found to mediate chemoresistance via different mechanisms in various cancers (Fig. 7).

CONCLUSIONS AND FUTURE APPROACHES

- EMT and MET are key players in regulating cellular plasticity in cancer, contributing to tumour progression, metastasis and resistance to therapy. Inhibiting EMT represents an attractive therapeutic approach, but challenges include:
  - Complexity of signalling pathways
  - Block particular pathways to seek the highest effectiveness and minimal toxicity
  - Cervical carcinoma metastasis and recurrence accounts for the majority of the related deaths and cannot be predicted due to the lack of early-stage biomarkers
  - AEG-1 has been implicated in tumour progression and chemoresistance in several malignancies, including cervical cancer. However, a better understanding of the molecular mechanisms of the AEG-1-induced EMT will be further elucidated.
  - Yet, future research should be addressed in two main streams:
    - Establishing AEG-1 as a reliable prognosis biomarker by evaluating sensitivity and specificity
    - Targeting AEG-1-induced EMT to halt cancer carcinoma progression and chemoresistance. Possible strategies include:
      - Gene silencing via RNA interference technology (siRNAs and microRNAs)
      - Identifying functional domains in AEG-1 to develop novel small molecule inhibitors
      - Immunotherapy (anti-AEG-1 antibodies)

GLOSSARY

- MMPI: Matrix metalloproteinases
- NF-κB: Nuclear Factor-κB
- CD20: Cyclin-dependent kinase 2
- LHD: Lung homing domain
- P13K: Phosphatidylinositol-3-kinase
- CCL20: Chemokine (C-C motif) ligand 20
- LC3B: Cytoskeletal-associated protein 1A/1B-light chain 3

REFERENCES