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In vitro susceptibility to the pro-apoptotic effects of TIMP-3 gene delivery translates to greater in vivo efficacy versus gene delivery for TIMPs-1 or -2

- Katherine M. Finan
  Katherine M. Finan
  Affiliations
  Department of Thoracic Medicine and Lung Research Laboratory, Royal Adelaide Hospital and Hanson Institute, Adelaide, South Australia 5000, Australia
  Search for articles by this author
- Greg Hodge
  Greg Hodge
  Affiliations
  Department of Thoracic Medicine and Lung Research Laboratory, Royal Adelaide Hospital and Hanson Institute, Adelaide, South Australia 5000, Australia

  Department of Haematology, Women's and Children's Hospital, Adelaide, South Australia 5000, Australia

  University of Adelaide, Adelaide, South Australia 5000, Australia
  Search for articles by this author
- Ann M. Reynolds
  Ann M. Reynolds
  Affiliations
  Department of Thoracic Medicine and Lung Research Laboratory, Royal Adelaide Hospital and Hanson Institute, Adelaide, South Australia 5000, Australia
  Search for articles by this author
- Sandra Hodge
  Sandra Hodge
  Affiliations
  Department of Thoracic Medicine and Lung Research Laboratory, Royal Adelaide Hospital and Hanson Institute, Adelaide, South Australia 5000, Australia
  Search for articles by this author
- Mark D. Holmes
  Mark D. Holmes
  Affiliations
  Department of Thoracic Medicine and Lung Research Laboratory, Royal Adelaide Hospital and Hanson Institute, Adelaide, South Australia 5000, Australia

  University of Adelaide, Adelaide, South Australia 5000, Australia
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  Andrew H. Baker
  Affiliations
  University of Glasgow, Glasgow, UK
  Search for articles by this author
- Paul N. Reynolds
  Paul N. Reynolds
  Correspondence
  Corresponding author. Tel.: +61 8 8222 5376; fax: +61 8 8222 5957.
  Contact
  Affiliations
  Department of Thoracic Medicine and Lung Research Laboratory, Royal Adelaide Hospital and Hanson Institute, Adelaide, South Australia 5000, Australia

  University of Adelaide, Adelaide, South Australia 5000, Australia
  Search for articles by this author

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In vitro susceptibility to the pro-apoptotic effects of TIMP-3 gene delivery translates to greater in vivo efficacy versus gene delivery for TIMPs-1 or -2

Previous ArticleUp-regulation of focal adhesion kinase in non-small cell lung cancer
Next ArticleLKB1 mutation in large cell carcinoma of the lung

Summary

Matrix metalloproteinases (MMPs) are essential for extracellular matrix (ECM) breakdown and repair, and have been implicated in the development of metastases. TIMP-3 was initially identified as a potent inhibitor of MMPs, however it also has several properties that are unique and not related to its ability to abrogate MMPs. We studied the effects of overexpression of tissue inhibitor of metalloproteinases-3 (TIMP-3) on lung cancer cells and explored the mechanisms involved in apoptosis-induction in susceptible cells and subsequently, the therapeutic effect in vivo. Overexpression of TIMP-3 resulted in apoptosis of A549 lung cancer cells and AdCMVTIMP3 up-regulated the expression of p53, Fas ligand, TNFR1 and TNFR2 on these cells. Adenoviral delivery of TIMP-3 gene inhibited the growth of pre-established A549 tumours in Balb/c nude mice, and was associated with a greater therapeutic effect than either TIMP-1 or -2 gene delivery. There was no evidence of increased hepatic toxicity following the delivery of TIMP-3 either from intra-tumoural or intravenous injection. Thus, at least in cells showing in vitro susceptibility, TIMP-3 gene therapy offers a therapeutic advantage over TIMPs 1 and 2. These findings establish the potential of adenoviral gene delivery of TIMP3 as a therapeutic agent for selected lung cancers.

Keywords

- Lung cancer
- Gene therapy
- TIMP-3
- Apoptosis
- A549 lung cancer cell line
- Subcutaneous lung cancer nodules

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    The authors regret that Fig. 8 was noted to inadvertently contain duplicate panels that were labeled as different treatment groups. A correct panel is provided: Effect of AdCMVTIMP3 on apoptosis by TUNEL assay. (1-a) PBS, (1-b) AdCMVLuc, (1-c) AdCMVTIMP-1, (1-d) AdCMVTIMP-2, (1-e) AdCMVTIMP-3.
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