EXPRESSION OF HTRA1, 2 AND 3 IN HUMAN ENDOMETRIAL CANCER

M. A. Bowden[1], *L. A. Di Nezza*[1], *T. Jobling*[2], *L. A. Salamonsen*[1], *G. Nie*[1]

[1]**Obstetrics and Gynaecology, Prince Henry's Institute of Medical Research, Clayton, VIC, Australia;**
[2]**Obstetrics and Gynaecology, Monash Medical Centre, Clayton, VIC, Australia**

The mammalian HtrA family consists of serine proteases with distinct domains homologous to the bacterial high temperature requirement factor (HtrA). Three human HtrA members have been reported: HtrA1 (PRSS11 or L56), HtrA2 (OMI) and HtrA3 (PRSP). The function of HtrA1 is not well characterised, but it has been shown to be downregulated in malignant tissues (1–3) indicating that the downregulation of HtrA1 is associated with cancer progression. HtrA2 regulates apoptosis by interacting with X-linked inhibitors of apoptosis (XIAP) thus preventing the caspase-inhibitory function of XIAP (4). The function of newly identified HtrA3 is not known, however it shares a high degree of sequence and domain homologies with HtrA1 and may therefore share a functional similarity with HtrA1 (5). Endometrial cancer (EC) is a prevalent gynaecological cancer, commonly affecting women after menopause. In this study we examined the expression of HtrA1, 2 and 3 in EC. Reverse transcriptase-PCR (semi-quantitative) analysis showed decreased mRNA expression of both HtrA1 and HtrA3, but no significant change for HtrA2, in EC tissue samples compared to normal endometrium. We then determined the protein level of expression and the cellular localisation of all three HtrA members in EC progression using immunohistochemistry. HtrA1 and HtrA3 showed a similar pattern of expression and both decreased dramatically with the progression of cancer from grade 1 through to 3. Surprisingly, HtrA2 protein expression was also decreased with cancer progression, but the decline was not as dramatic as that for HtrA1 and HtrA3. Interestingly, considerably less staining was observed for all three HtrA proteins in grade 3 cancer tissues. These data suggest that decreased expression of HtrA proteins, particularly HtrA1 and HtrA3, is associated with the progression of endometrial cancer.

(1) Nie, G., Hampton, A., Li, Y., Findlay, J., Salamonsen, L.A. (2003) Identification and cloning of two isoforms of human high-temperature requirement factor A3 (HtrA3), characterization of its genomic structure and comparison of its tissue distribution with HtrA1 and HtrA2. *Biochem. J.* **371**, 39–48. (2) van Loo, G., van Gurp, M., Depuydt, B., Srinivasula, S.M., Rodriguez, I., Alnemri, E.S., Gevaert, K., Vandekerckhove, J., Declercq, W., Vandenabeele, P. (2002) The serine protease OMI/HtrA2 is released from mitochondria during apoptosis. OMI interacts with caspase-inhibitor XIAP and induces enhanced caspase activity. *Cell Death Diff.* **9**, 20–26. (3) Chien, J., Staub, J., Hu, S., Erickson-Johnson, M.R., Couch, F.J., Smith, D.I., Crowl, R.M., Kaufmann, S., Shridhar, V. (2004) A candidate tumour supressor HtrA1 is down-regulated in ovarian cancer. *Oncogene* **23**, 1636–1644. (4) Shridhar, V., Sen, A., Chien, J., Staub, J., Avula, R., Kovats, S., Lee, J., Lillie, J., Smith, D.I. (2002) Identification of underexpressed genes in early- and late-stage primary ovarian tumours by suppression subtraction hybridization. *Cancer Res.* **62**, 262–270. (5) Baldi, A., De Luca, A., Morini, M., Battista, T., Felsani, A., Baldi, F., Catricala, C., Amantea, A., Noonan, D. M., Albini, A., Ciorgio, P., Lombardi, D., Paggi, M. G. (2002) The HtrA1 serine protease is down-regulated during human melanoma progression and represses growth of metastatic melanoma cells. *Oncogene* **21**, 6684–6688.

10.1071/SRB04Ab284