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IL-1α gene expression in human endometrial cancer is independent of ovarian steroid receptor expression

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Interleukin-lα (IL-1α) is known to play a pivotal role in human physiology and reproduction. In the cycling endometrium, IL-1α activity is controlled by local oestrogen and progesterone concentrations and is restricted to the perimenstrual phase where it is involved in the regulation of tissue-lytic enzymes such as the matrix metalloproteinase-1 (MMP-1) [1]. Release and subsequent activation of MMP-1 and other matrix metalloproteinases by the endometrial stroma ultimately results in local tissue lysis and menstrual bleeding and menstruation [2,3]. Since local tissue degradation is also a feature of many malignancies, we have analysed the gene expression of IL-1α and other members of the interleukin-1 family in 27 endometrial cancers, and compared it to *oestrogen receptor α, oestrogen receptor β* and *progesterone receptor* mRNA expression [4,5]. These members include the interleukin-1β (IL-1β) which—similar to IL-1α—is able to bind and to activate the IL-1 receptor; the complete interleukin-1 receptor antagonist (IL-1Ra) and the interleukin-1 type I receptor (IL-1t1)—which is the signal transducing transmembranous protein. Endometroid tumour tissues were obtained during hysterectomy for endometrial cancer and the gene expression of each factor was investigated by reverse transcriptase-polymerase chain reaction (RT-PCR). Furthermore, protein expression and the spatial orientation of IL-α was detected by immunohistochemical staining. We found a strong *IL-1t1* and *oestrogen receptor α* gene expression was present in all tissues analysed, regardless of their histology and differentiation. We also detected variable amounts of *IL-1β* and *IL-1Ra* mRNA in the vast majority of samples. Here again, no correlation was found with the degree of differentiation. Conversely, *IL-1α* and *oestrogen receptor β* gene expression were considerably less frequent with *IL-1α* being absent in all but one of the well differentiated (GI) tumours. With decreasing differentiation (G2 and G3), *IL-1α* gene expression became more common. We did not, however, find an inverse correlation between the expression of *IL-1α* and oestrogen receptor gene expression, although *IL-1α* mRNA expression in endometrial cancers was clearly correlated to *IL-1β* gene expression. At the protein level, *IL-1α* was immunodetected predominantly in epithelial tumour cells of lower grade tumours, although some weak fibroblastic staining was also seen in a few cases. Taken together, we have demonstrated the presence of the IL-1 system in endometrial malignancies and found a negative correlation between *IL-1α* and tumour differentiation. Epithelial tumour cells were identified as the source of tumoral IL-1α protein. Furthermore, the expression of IL-1α mRNA was independent of the oestrogen receptor status, thus indicating that in the malignant endometrium the suppressive effect of ovarian steroids on the IL-1α gene and protein expression is no longer functional. We hypothesise that the non-physiological expression of IL-1α in less differentiated tumours might contribute to their invasiveness and malignant behaviour, presumably through the IL-1α-induced expression of matrix degrading enzymes such as MMP-1 [6].

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