

Cytokine Networks in Endometrial Carcinogenesis

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Endometrial cancer (EC) is the commonest gynaecological malignancy in the developed world and falls into two categories. Type I (~75% cases) is generally oestrogen-sensitive, develops from premalignant hyperplasia and is low-medium grade. By contrast, the rarer high grade Type II is frequently oestrogen receptor negative, have no premalignant lesion and have poorer outcomes. This study characterised cytokine-based microenvironmental features associated with endometrial carcinogenesis given their role in immunoregulation and tumour behaviour.

Endometrial lysates (38 normal, 25 hyperplastic and 97 cancerous; 46 Type I, 51 Type II) were profiled for 49 cytokines by multiplex immunoassay which were then standardised against total protein. Data were analysed by Kruskal-Wallis tests with Mann-Whitney-*U* tests *post hoc*, applying False Discovery Rate correction for multiple comparisons. The *R* package *Catnet* was used for learning categorical Bayesian networks, where data were fitted according to Maximum Likelihood Estimation-based network search by Simulated Annealing without a prior seed network. Final networks were selected based on maximal Akaike information criterion values and visualised in Gephi.

Significant differences in the concentration of 28 cytokines were noted between the groups. Cytokine profiles matched the robust histology-based discrimination between normal, hyperplastic and cancerous endometrial tissues, including differentiating between Type I/II cancers. These differences were also reflected in cytokine interrelationships; distinct subnetworks with different nodal foci were seen across all groups. In particular, GM-CSF appeared to play a major regulatory role uniquely in normal endometrium. However, the hub node function of other mediators was more conserved: IL-17 was consistently found in this capacity in all categories except Type II ECs, which instead favoured IL-4 and IFN- γ . Moreover, a central role for agents such as TNF- α was only seen in cancers.