1- Current concepts in the pathology and epigenetics of endometrial carcinoma

In the Western world, endometrial carcinoma is the most common malignant tumour of the female genital tract and is the fourth most common cancer in women. Two different clinicopathological subtypes are recognised: the oestrogen-related (type I, endometrioid) and the non-oestrogen related (type II, non-endometrioid). This article reviews the epidemiology, risk factors, genetic alterations during endometrial carcinogenesis, features of tumours and precursors and early detection of the disease. Insights into the epigenetic alterations, with emphasis on DNA methylation during endometrial carcinogenesis, and their diagnostic value are also provided

2- Characterization of hepatitis C virus-induced nasal mucosa remodelling

No abstract available

3- Progression model tissue microarray (TMA) for the study of uterine carcinomas

Cervical and endometrial uterine carcinomas are heterogeneous groups of cancers, which are preceded by preneoplastic lesions. More accurate tools are needed to improve the diagnosis and to define markers which may be relevant for the diagnosis, prediction of disease progression and therapeutic response. High throughput technologies for testing and validating molecular targets in cancer lesions and in their precursors are presently available. Among them, the tissue microarray (TMA) presents the advantage of a morphological control of the analyzed tissue fragment. In this article, we review the different aspects of the TMA technology with a special consideration to a uterine carcinogenesis model.

4- Local applications of GM-CSF induce the recruitment of immune cells in cervical low-grade squamous intraepithelial lesions

PROBLEM: Quantitative alterations of antigen-presenting cells (APC) in (pre)neoplastic lesions of the uterine cervix associated with human papillomavirus (HPV) infection suggest a diminished capacity to capture viral antigens and to induce a protective immune response.

METHOD OF STUDY: To test whether a cervical application of GM-CSF could restore an immune response against HPV in women with cervical low-grade squamous intraepithelial lesions (LSIL), we performed two clinical trials with 11 healthy women and 15 patients with LSIL.

RESULTS: GM-CSF applications were well tolerated in all enrolled women, and no difference in toxicity between the treated and placebo groups was observed during the follow-up (until 30 months). Interestingly, in the GM-CSF treated group, a significant increase of APC and cytotoxic T-lymphocyte infiltration was observed in the cervical biopsies with no change in regulatory T cell numbers. All the HPV16(+) patients exhibited an immune response against HPV16 after GM-CSF applications, as shown by NK and/or T cells producing IFN-gamma whereas no cellular immune response was
observed before the treatment. Moreover, the anti-virus-like particles antibody titers also increased after the treatment.

CONCLUSION: These encouraging results obtained from a limited number of subjects justify further study on the therapeutic effect of APC in cervical (pre)neoplastic lesions.

5-

**Combined analysis of HPV DNA, p16, p21 and p53 to predict prognosis in patients with stage IV hypopharyngeal carcinoma**

PURPOSE: We examined p16, p21 and p53 expression in combination with the presence of human papillomavirus (HPV) DNA as molecular markers to predict survival in patients with stage IV hypopharyngeal squamous cell carcinoma (HSCC).

METHODS: Paraffin-embedded tumours from HSCC patients (n = 75) were evaluated for p16, p21 and p53 expression by immunohistochemistry. HPV DNA was detected by GP5+/6+ consensus PCR and subsequent genotyping by E6/E7 type-specific PCR for HPV types 6, 11, 16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66 and 68.

RESULTS: Among the 61 specimens that tested positive for the δ-globin, HPV typing identified 50 patients with high-risk (hr) HPV types. HPV 16E7 DNA was detected in 74% (37 cases) of these specimens. Twelve patients were found to be infected with multiple HPV types. However, the presence of hrHPV DNA was not found to correlate with the proportion of disease-free patients. The 5-year disease-free survival rate was 73% in p53- tumours versus 48% in p53+ tumours (P = 0.008).

CONCLUSION: In our series of patients with stage IV HSCC, the hrHPV+ subgroup had a similar prognosis (in terms of recurrence risk) as the HPV- subgroup. p53 overexpression was associated with a worse prognosis

6-

**Lactate dehydrogenase-B is silenced by promoter methylation in a high frequency of human breast cancers**

OBJECTIVE: Under normoxia, non-malignant cells rely on oxidative phosphorylation for their ATP production, whereas cancer cells rely on Glycolysis; a phenomenon known as the Warburg effect. We aimed to elucidate the mechanisms contributing to the Warburg effect in human breast cancer.

EXPERIMENTAL DESIGN: Lactate Dehydrogenase (LDH) isoenzymes were profiled using zymography. LDH-B subunit expression was assessed by reverse transcription PCR in cells, and by Immunohistochemistry in breast tissues. LDH-B promoter methylation was assessed by sequencing bisulfite modified DNA.

RESULTS: Absent or decreased expression of LDH isoenzymes 1-4, were seen in T-47D and MCF7 cells. Absence of LDH-B mRNA was seen in T-47D cells, and its expression was restored following treatment with the demethylating agent 5â€™Azacytidine. LDH-B promoter methylation was identified in T-47D and MCF7 cells, and in 25/25 cases of
breast cancer tissues, but not in 5/5 cases of normal breast tissues. Absent immuno-expression of LDH-B protein (CONCLUSIONS:
Loss of LDH-B expression is an early and frequent event in human breast cancer occurring due to promoter methylation, and is likely to contribute to an enhanced glycolysis of cancer cells under hypoxia.

7-
**Novel association between vasoactive intestinal peptide and CRTH2 receptor in recruiting eosinophils: a possible biochemical mechanism for allergic eosinophilic inflammation of the airways**

We explored the relation between vasoactive intestinal peptide (VIP), CRTH2, and eosinophil recruitment. It is shown that CRTH2 expression by eosinophils from allergic rhinitis (AR) patients and eosinophil cell line (Eol-1 cells) was up-regulated by VIP treatment. This was functional and resulted in exaggerated migratory response of cells against PGD2. Nasal challenge of AR patients resulted in a significant increase of VIP contents in nasal secretion (ELISA), and the immunohistochemical studies of allergic nasal tissues showed significant expression of VIP in association with intense eosinophil recruitment. Biochemical assays showed that VIP-induced eosinophil chemotaxis from AR patients and Eol-1 cells was mediated through the CRTH2 receptor. Cell migration against VIP was sensitive to protein kinase C (PKC) and protein kinase A (PKA) inhibition but not to tyrosine kinase or p38 MAPK inhibition or calcium chelation. Western blot demonstrated a novel CRTH2-mediated cytosol-to-membrane translocation of PKC-$\mu$, PKC-$\gamma$, and PKA-$\alpha$, $\pm$,- and -II$\pm$-reg in Eol-1 cells upon stimulation with VIP. Confocal images and FACS demonstrated a strong association and co-localization between VIP peptide and CRTH2 molecules. Further, VIP induced PGD2 secretion from eosinophils. Our results demonstrate the first evidence of association between VIP and CRTH2 in recruiting eosinophils.

8-
**IFN-$\gamma$ and TNF-$\alpha$ potentiate prostaglandin D2-induced human eosinophil chemotaxis through up-regulation of CRTH2 surface receptor.**

Prostaglandin D2 (PGD2) receptor CRTH2, is a pro-inflammatory molecule involved in eosinophil recruitment to the allergic airway. We investigated the expression of CRTH2 in eosinophil from allergic rhinitis patients (AR) and tested the modulatory role of several TH1 and TH2 cytokines closely related to the allergic immunological response, on the expression of CRTH2 receptor, utilizing human eosinophil cell line (Eol-1). The expression of CRTH2 was tested by immunohistostaining and flow cytometry (FACS). Chemotaxis was performed in micro-chemotaxis chambers. It is shown that the expression of CRTH2 by eosinophils was significantly higher in the nasal tissue and peripheral blood of AR patients, when compared to control subjects. PGD2 exhibited a typical bell shape dose response in attracting eosinophil from AR patients with optimal activity at 10(-7) M. Eol-1 cell surface expression of CRTH2 was significantly up-regulated by 10 ng/ml IFN-$\gamma$ and TNF-$\alpha$. The percentage of Eol-1 cells expressing the receptor increased by IFN-$\gamma$ and TNF-$\alpha$ from 12.74%±2.66 to 55%±8 and 33.8%±9.4, respectively. PGD2-induced Eol-1 chemotaxis was not blocked by SB203580, H-89 Dihydrochloride, Bisindo-lylmaleimide, or Genistein. PGD2-induced
Eol-1 chemotaxis was potentiated by IFN-\(\text{\textgreek{x}}\) and TNF-\(\text{\textgreek{x}}\) \(\pm\) without changing the signal transduction pathway. Correlation of our results to peripheral blood eosinophils from allergic rhinitis patients confirmed that 3 hour pretreatment of eosinophils by 10 ng/ml IFN-\(\text{\textgreek{x}}\) and TNF-\(\text{\textgreek{x}}\) \(\pm\), increased the mean fluorescence intensity (MFI) of CRTH2 from 8.23 to 9.68 and 9.38, respectively, and potentiated PGD2-induced eosinophil chemotaxis. Our results demonstrate a novel synergism between PGD2, IFN-\(\text{\textgreek{x}}\) and TNF-\(\text{\textgreek{x}}\) \(\pm\), in eosinophil chemotaxis.

9. **Virus-induced cancers: interplay between genetics and environment**

Among cancers diagnosed worldwide on a yearly basis, 20% are thought to be associated with a viral infection. The viruses involved are, by order of decreasing incidence, the hepatitis viruses, the papillomaviruses and the Epstein-Barr virus. These virus-induced cancers generate a high level of interest not only for the study of mechanisms involved in the neoplastic transformation, but also for the set-up of specific immunotherapies including prophylactic and therapeutic antitumor vaccination.