

Cervical Intraepithelial Neoplasia- Predictive molecular growth factors in natural history

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There is considerable controversy regarding the possible over-treatment of patients with mild Cervical intraepithelial neoplasia (CIN), with lesions being often excised or ablated. Thus, identifying the markers of potentially malignant lesions would be of a great prognostic value. In the current study, we hypothesized that using colposcopic, cytological and histological findings together with assessing the expression of molecular growth factors can predict CIN outcome. The study group consisted of 285 women between 19 and 81 years of age (median age, 37, 8 years). The follow up were 60 months and considered 138 women: 50 women with Subclinical papillomavirus infection (SPI), 50 women with CIN1 and 38 women with CIN2.

All patients underwent cytology, colposcopy, and sampling for subsequent testing for HPV. In cases in which colposcopy suggested the presence of suspicious lesions, biopsy specimens were taken. HPV DNA was genotyped for HPV types 16, 18, 31, 33, and 45 by multiplex PCR. Transcripts of HR HPV types 16, 18, 31, 33, and 45 were detected by the NucliSens EasyQ HPV assay. The VEGF expression was analyzed with immunohistochemistry, RNA extraction, cDNA synthesis and RT-PCR analysis and Western blot.

We found that so called lymphangiogenetic switch (over expression of VEGF C and VEGFR-2) appears already in CIN 2, which is a rare observation, Persistent HPV HR infection is not only a trigger but also a maintenance factor in the cervical carcinogenesis. CIN2/3 and cervical cancer is in high percentage associated with the presence of HR DNA HPV as well as E6/E7 DNA mRNA.

In CIN2/3 and cervical cancer VEGF and its receptor expression correlate with the stage of cervical carcinogenesis.

Progression of cervical intraepithelial neoplasia occurs when co expression of all : HR DNA HPV, E6/E7 HR HPV mRNA and VEGF is present.

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Hyperdiploid tumors as a driving force in genomic instability

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In this lecture we address attention to human breast tumor progression during continuously increasing genomic instability reflected in three ploidy entities. These entities are identified based on DNA-Index (DI) intervals as diploid (D-type-), tetraploid (T-type) and aneuploid tumors (A-type). Following increase in genomic instability and proliferative activity as a reference in a simulation a transition from D-type to T-type tumors was found and a subsequent turn over to A-type tumors. In the breast tumors analyzed this occurred particularly in a limited tumor size interval between 10 to 20 mm. The parameter used to reflect genomic instability we have defined as Stemline-scatter-index (SSI). It includes the addition of the parameters of G1-coefficient of variation, percentage of S-phase fraction and the percentage of exceeding G2 cells based on image analysis of Feulgen stained tumors cells. After the invasiveness of the tumor and increasing SSI values T-type tumors seem to lose DNA-content and become included in the A-type DI region. When established as a solid growing tumor an increasing anoxia has been reported in the literature as a driving force for genomic instability. Reaching the tumor size interval of 10 to 20 mm a new wave of T-type tumors was observed. We found these T-type tumors to be recruited from a hyper-diploid (D-type) population within a relatively narrow DI interval. We deduced this to be caused by increasing anoxia due to lack of enough blood vessel in-growth, a theory well established in the literature. In the next and final interval of high SSI values the A-type tumors dominated the tumor population.

Biography

Roland B Sennerstam entered research in the seventies at the Institution of Cell Research at the laboratory of Professor Torbjörn Caspersson Karolinska Institutet. In his research, he has focused on the proliferation of the cell cycle and the development of tumors during increasing genomic instability. In the nineties he developed a model for the cell cycle together with Professor Jan-Olov Strömberg and a computer simulating program was created where several parameters could be analyzed over many cell generations. Lately he has focused on growth and development of breast cancer related to genomic instability.