

Cervical cancer

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COLUMNAR EPITHELIUM IS THE ORIGINAL SITE OF MOST CERVICAL SQUAMOUS CELL CANCERSOlaf Reich, Sigrid Regauer. *Medical University of Graz, Graz, Austria*

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Introduction/Background Cervical HPV-research is based on mature squamous epithelium (Woodman, CB. *Nat Rev Cancer* 2007), however, only a minority of squamous cell cancer (SCC) arise in this type of epithelium. Surprisingly, it was only in the last years that immature squamous metaplastic epithelium in the transformation zone and reserve cells (RC) throughout the columnar epithelium moved into research focus.

Methodology This review will focus on recent aspects of HPV-induced cervical carcinogenesis.

Results UGS-derived p63/CK17-positive RC located within the columnar epithelium are precursor cells for metaplastic squamous epithelium and subsequent HSIL and SCC (Fritsch, *Clin Ant* 2021; Regauer S. *Curr Opin Virol* 2021). RC may be target for HPV-infection and act as reservoirs of HPV (Goyal A, *Am J Surg Path* 2020; Doorbar J, *Curr Opin Virol* 2021). A HPV-infection of proliferating RC and immature metaplasia that is not controlled by the immune system, allows development of small foci of thin HSIL as result of inhibition of p53- and Rb-protein-mediated cell-cycle processes by E6/7-protein (Reich, *Int J Gynecol Pathol* 2017; Regauer, *Am J Surg Pathol* 2021; Regauer, *Curr Opin Virol* 2021). Enlargement of thin HSIL and stepwise progression from thin to thick HSIL eventually produce larger lesions, and invasion begins from thick HSIL inside the TZ.

Conclusion Contrary to the prevailing opinion, cervical SCC arise most frequently from RC and immature metaplastic epithelium in the TZ. Cervical carcinogenesis is not limited to the SCJ, and cuboidal cells, that accomodates for the difference of epithelial thickness at the SCJ, are of no significance for carcinogenesis.

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DIFFERENTIATED CERVICAL INTRAEPITHELIAL NEOPLASIA (D-CIN) REPRESENTS A RARE HPV-INDEPENDENT PRECURSOR LESION OF SQUAMOUS CELL CANCEROlaf Reich, Sigrid Regauer. ¹*Medical University of Graz, Graz, Austria;* ²*Medical University Graz, Graz, Austria*

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Introduction/Background Although our knowledge of HPV-independent squamous cell cancers (SCC) of the cervix is growing, the current 2020 WHO classification does not describe HPV independent cervical precancers. The main reason for this was that these exceedingly rare cervix HPV-independent precancerous lesions were not described at time of publication.

Methodology This review will focus on recent aspects of HPV-independent cervical carcinogenesis.

Results In 2020 we reported for the first time a preinvasive cervical lesion negative with 3 different HPV tests in a series of 474 cone specimens (Reich O. *Gynecol Oncol* 2020). In 2022 we demonstrated detailed characteristics of HPV-negative cervical intraepithelial precursors (Regauer S. *Am J Surg Path* 2022). HPV-negativity was defined as lack of both, DNA of 32 HPV subtypes and E6/E7 mRNA of 14 HPV subtypes, and additionally by the absence of HPV sequences in ~5 Mio's WGS reads. The morphological hallmark of this cervical lesion was the presence of atypical keratinocytes confined to the basal and parabasal layers in squamous epithelium with hyper- and parakeratosis with elongated rete ridges. The subepithelial stroma had a dense inflammation with plasma cells and eosinophilic granulocytes. Finding an appropriate terminology for these differentiated intraepithelial precursor lesions, however, proves difficult. In analogy to terminology of vulvar carcinogenesis, differentiated cervical intraepithelial neoplasia (d-CIN) may be appropriate.

Conclusion The existence of primarily HPV-negative squamous cervical precancers (d-CIN type and basaloid type) needs to be recognized (Regauer S. *Int J Gynecol Cancer* 2022). In a future classification squamous intraepithelial cervical precancers should be grouped into two categories: HPV-associated and HPV-independent.

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GENOMIC CHARACTERISTIC ANALYSIS IN SQUAMOUS CELL CARCINOMA AND ADENOCARCINOMA OF CERVIX IDENTIFIES ALPELISIB AS A THERAPEUTIC OPTION FOR PIK3CA MUTATIONAL CERVICAL CARCINOMACanhui Cao, ¹Ye Wei, ¹Shitong Lin, ¹Binhan Liu, ²Sheng Cheng, ²Zhixian Zhu, ¹Peng Wu. ¹*Tongji Medical College of Huazhong University of Science and Technology: Huazhong University of Science and Technology Tongji Medical College, Wuhan, China;* ²*National Key Laboratory of Crop Genetic Improvement, Huazhong Agricultural University, Wuhan, China*

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Introduction/Background Cervical squamous cell carcinoma (CSCC) and cervical adenocarcinoma (CAcC) are the two most histological types in cervical carcinoma, with unequal outcomes and unclear mechanisms in tumor biology. We aim to explore the genomic characteristics between them and identify a promising target for cervical carcinoma.

Methodology We analyzed the genomic data of cervical carcinoma to identify genomic characteristics between SCC and CAcC. *In vitro* and *in vivo* assays were performed to testify the therapeutic effects of Alpelisib in PIK3CA mutational cervical carcinoma. Mutation analysis, Enrichment and pathway analysis, and co-immunoprecipitation were used to demonstrate the mechanisms of Alpelisib in cervical carcinoma.

Results CSCC showed higher point mutation density, high copy number cluster, low to intermediate CpG island methylator phenotype (CIMP) compared with CAcC, with the enrichment in the RTK/PI3K/MAPK pathway. In addition, point mutation of PIK3CA (P=0.0401) was significantly observed in CSCC, with different overall survival (P=0.0469) between the two histological types. *In vitro*, PIK3CA mutational cell lines (ME-180 and Ca-Ski) showed higher sensitivity to Alpelisib than cell lines without PIK3CA mutation. The correlation genes of PIK3CA in cervical cancer showed the enrichment of