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CHARACTERIZATION OF EPITHELIAL LINING OF NORMAL AND PRECANCEROUS UTERINE CERVIX IN MICE

by

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Abstract

Despite the fact that cervical cancer is a common health issue among women worldwide, little is known regarding the epithelial lining of the uterine cervix where cancer originates. In general, cancer development involves alterations in glycoconjugate expression and changes in the dynamics of cellular proliferation and differentiation. Therefore, the aims of this study were to define carbohydrate moieties and cellular dynamics of the epithelial lining of the uterine cervix in normal mice and then in mice developing cervical precancerous lesions. Since the uterus undergoes cyclic changes, mice in each of the four stages of the estrus cycle were first identified using both vaginal cytology and histological examination of the vaginal epithelium. Tissue sections of the uterine cervix from mice at proestrus, estrus, metestrus, and diestrus stages were processed for incubation with a panel of 20 lectins specific to different N- and O-linked oligosaccharides. Several lectins specific for different glycoconjugates were found to label different regions of the cervical epithelium. *Lycopersicon esculentum* lectin specific for N-acetyl-glucosamine was found to bind to the basal layer of the stratified epithelium of ectocervix and the stratified part of endocervix during proestrus and estrus stages. *Erythrina cristagalli* lectin specific for galactose bound to the apical surface of the columnar cells of endocervix during the proestrus stage. Several lectins including soybean agglutinin, *Ulex europaeus* agglutinin I, and *Lens culinaris* lectins, respectively specific for N-Acetyl-galactosamine, fucose, mannose/glucose, recognized the apical mucous layer of ectocervix during the diestrus stage. Glycoconjugate expressions were correlated with cervical epithelial cell dynamics which were studied using bromodeoxyuridine by single injection, multiple injections, and continuous infusion followed by immunohistochemistry. Proliferating cells were confined to the basal layer of ectocervix and the stratified part of endocervix but were scattered along the columnar cells of endocervix. Quantitative analysis showed that the life span of cervical epithelial cells was very short, 4-5 days. For the second aim, a mouse model for cervical precancerous lesions was developed using prenatal injections of diethylstilbestrol. Adult female offsprings were examined at 2- and 4-month-old. Diethylstilbestrol induced a block in the estrus cycle with persistent vaginal and ectocervical cornification similar to estrus stage. The 2-month-old mice developed festooned endocervical epithelium with pseudostratified or even stratified patches. These early metaplastic changes were associated with an increase in the percentages of bromodeoxyuridine labeled cells in the epithelial lining of both ectocervix and endocervix. At 4 months, the lining of endocervix was entirely transformed into stratified squamous epithelium with intraepithelial adenosis. These precancerous changes were associated with an upregulation of the transcription factor p63 in the endocervix with multiple alterations of lectin binding specificity. The results suggest that lectins *Lycopersicon Esculentum*, *Ulex europaeus* and *Arachis hypogaea* respectively specific for N-Acetyl-glucosamine, fucose, and galactose are potential markers for precancerous changes in the mouse uterine cervix. In conclusion, data obtained from this study will help in identifying new targets for early detection and therapy of cervical cancer in preclinical studies.

Keywords: Uterine cervix, cervical cancer, estrus cycle, lectins, cell proliferation, diethylstilbestrol.