06 July 2008 **08:00 - 08:50**

EDUCATIONAL LECTURE

Viruses and cancer

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The pathogenesis of human papillomaviruses associated cancers - theoretical concepts and clinical applications

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Persistent infections with 15 high risk types of the human papillomaviruses (HR-HPV) are associated with malignant transformation of epithelial cells particularly at the transformation zone of the uterine cervix, but less common also at other anatomical sites. HR-HPVs encode two viral genes that confer numerous oncogenic features to normal replicating cells under experimental conditions. These are due to interactions with various host cell proteins among them the p53 and pRB tumor suppressor proteins. Despite the very well documented oncogenic features of these HR HPV types, infections with these viruses are very common and usually not associated with relevant disease in men and women. This is due to the fact that the expression of viral genes in the epithelial host cells is precisely regulated in a differentiation dependent manner. Three distinct types of infection can be differentiated primarily based on the expression pattern of the HPV genomes in the infected epithelial cells: These are best described as latent, replicating, and transforming infections. The latent infection is induced upon entry of the virus into basal cells of the epithelium. During this stage no major viral gene expression is observed in none of the epithelial cell layers. Latent infected cells may switch to acute replicating infections during that distinct genes of the virus are expressed primarily in differentiated cells of the intermediate and superficial cell layers. This allows for replication of the viral genome in intermediate and packaging and release of mature virus particles in the superficial cell layers of the infected epithelium. It is important to note that no major gene expression of the virus is observed in the basal and parabasal cells of the epithelium, the only cells that retain the capacity to proliferate and hence could conceptually be transformed by certain oncogenes. The acute infections may progress to transforming infections during that indeed expression of viral oncogenes is observed in the replication competent basal and parabasal cells of the epithelium. This results in chromosomal instability in the affected epithelial stem cells and finally provides the preconditions for the outgrowth of high grade dysplasia or invasive cancers. Consequently the switch from the acute replicating infections to the persistent transforming infections is the hall mark of HPV-induced dysplasia and its progression to invasive carcinomas. This is of particular diagnostic interest since the acute infections are very common particularly in younger adults and the detection of HR-HPV infections has not proven useful and cost effective in primary screening in women younger than 30.

Recently vaccines against some high risk and low risk HPV types have been developed and showed remarkable clinical efficacy in reducing the occurrence of HPV-related lesions in clinical trials. The success of these vaccines and their increasing use will bring up further novel demands for improved cervical cancer screening programs. Over the past years several novel biomarkers have been investigated that may allow for the specific detection of cells that display the deregulated type of HPV gene expression that is characteristic for transforming HPV infections. Various genetic alterations such as specific gains and losses of chromosomal material, integration of the viral genome, specific methylation patterns of cellular genes and many more have been investigated with regard to their diagnostic potential as suitable cancer early detection markers. Most of them however were rather late indicators of increasing chromosomal instability but not directly linked to the switch from the acute to the transforming HPV infection patterns. Based on the biochemical properties that are conferred by the HPV E7 oncoprotein the cyclin dependent kinase inhibitor p16INK4a is strongly over-expressed in virtually all cells that were transformed by oncogenic HPV types. This suggests that p16INK4a may represent an ideal biomarker for the detection of HPV transformed epithelia also under clinical conditions. Clinical studies on this novel concept suggest that biomarkers like p16INK4a will indeed help to overcome many important limitations of the present cervical cancer screening programs, particularly in a changing post-HPV vaccine world.

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EDUCATIONAL LECTURE

Biomarkers for tailored therapy

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Systems approach to drug development and implementation

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The realization of the promise of personalized molecular medicine will require the efficient development and implementation of novel targeted therapeutics. The goal will be to deliver the right drug to the right patient at the right time at the right dose. This effort will require a integration of information from the DNA, RNA and protein level into predictors of which patients are likely to respond to particular therapies. The overall likelihood of response to particular drugs represents the interaction between predictors of sensitivity with predictors of resistance. Efficient clinical trials testing these precepts will require the development and implementation of novel trial designs. It is likely that we will need to increase the size of phase I and II trials to allow the identification and validation of molecular markers at the same time as the initial evaluation the toxicity and efficacy of targeted therapeutics. This will come with the advantage of being able to deliver targeted therapeutics to enroll a much smaller population of patients selected for the likelihood to respond in phase III trials accelerating the approval of effective targeted therapeutics. The phosphatidylinositol 3'kinase (PI3K) pathway is aberrant at multiple levels across a wide variety of tumors making it the most common activating aberration in cancer. This has led to the development and now early clinical testing of drugs targeting multiple components of the pathway. The efficient utilization of these drugs will require the ability to accurately determine mutation and activation status in tumors as well as determining the interaction between the PI3K pathway and other pathways in driving tumor pathophysiology. Using a novel accurate and sensitive mass spectroscopy based sequencing approach, we have evaluated mutations in the PI3K pathway across more than 500 breast cancer samples. We have also implemented a high throughput functional proteomics approach designated reverse phase protein arrays to characterize the level and activity of multiple signaling pathways. We demonstrate than an integrated analysis of mutation, proteins levels and protein activity is able to predict lack of response to trastuzumab in patients and to novel drugs targeting the PI3K pathway in vitro. This demonstrates that the response to targeted therapeutics is due to an interaction of markers of sensitivity and markers of resistance and provides important approaches for patient selection. The PI3K pathway is critically important to cellular function and is thus under exquisite homeostatic control. The feedforward and feedback loops in the pathway determine the response to perturbation of the pathway by mutation or therapeutic intervention. Strikingly inhibition of the pathway at the level of mTOR or AKT results in the activation of potent feedback loops resulting in activation of multiple cell surface tyrosine kinases, PI3K itself and in the case of mTOR inhibitors, AKT. This may contribute to the observation that mTOR inhibitors appear to make some patient tumors grow more rapidly an unexpected and disappointing consequence of targeted therapeutics. Our preliminary systems biology-based mathematical and experimental models of the PI3K signaling network accurately predict these consequences as well as the biochemical processes involved. Further, the models suggest combinations of targeted therapeutics likely to reverse the negative effects of the mTOR inhibitors converting the outcome from negative to positive in terms of tumor growth. Systems biology is the study of the emergence of functional properties that are present in a biological system but that are not obvious from a study of its individual components. Systems biology is a data-driven process requiring comprehensive databases at the DNA, RNA, and protein level to integrate systems biology with cancer biology.