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SQUAMOUS DIFFERENTIATION IN HPV NEGATIVE AND POSITIVE KERATINOCYTES DETERMINES THE EXTENT OF INTERFERON-INDUCED GROWTH ARREST. Istvan Arany[1], Miriam M. Brysk[1,2], Henry Brysk[2] and Stephen K. Tyring[1,2], [1]Department of Microbiology and Immunology and [2]Department of Dermatology, The University of Texas Medical Branch, Galveston, Texas.

Previous studies suggest that interferon(IFN)-gamma plays a role in the regulation of proliferation and differentiation in the epidermis. *In vivo*, induction of differentiation proceeds by irreversible growth arrest and expression of squamous cell-specific genes. Nevertheless, many neoplastic cells have lost the ability to differentiate or their capability to differentiate is diminished as their malignant potential increases. This lack of differentiation potential can influence the effectiveness of IFN-mediated growth arrest and differentiation leading to IFN-resistance or unresponsiveness. In addition, presence of viral oncoproteins, such as human papillomavirus (HPV) early gene products (E6 or E7) can interact with both the cell differentiation and the IFN-driven signalling pathways. Accordingly, the aim of the present study was to determine the effects of a.) cell types, b.) malignant transformation, and c.) the presence of HPV oncoproteins on IFN-gamma-mediated growth arrest *in vitro*. RT-PCR was done to determine mRNA levels of various genes playing a role in regulation of cell proliferation (c-*myc*, cdc2 kinase, p53, RB,TGFβ1, gadd45, WAF-1, PKR), as well as markers of squamous differentiation (K10, involucrin) in various primary or established cultures of epithelial cells. Our results indicate that the effect of IFN-gamma on cell proliferation and differentiation is strictly cell-type specific and is determined by the ability of cells to terminally differentiate which can be affected by neoplastic phenotype or presence of HPV. These data could provide further details on molecular mechanisms of IFN-action.

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Antiviral Effect on Infectious Pancreatic Necrosis Virus Replication

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Infectious pancreatic necrosis virus is a member of the *Birnaviridae* family that causes one of the most serious diseases in trout and salmon farms around the world. It is also found in other fish species and shellfish. With the purpose of establishing an efficient anti-IPNV therapy we evaluated a group of compounds, that, based on the structural and functional IPNV characteristics, could possibly have antiviral activity. IPNV is a non-enveloped, single-shelled icosahedral virus, that possesses a bisegmented double-stranded RNA. Therefore, we selected for testing some compounds shown to have broad spectrum activity against both single- and double-stranded RNA viruses. The effect of antivirals was determined by a virus plaque inhibition assay. The IMP dehydrogenase inhibitors ribavirin and EICAR (5-ethynyl-1-ß-D-ribofuranosylimidazole-4-carboxamide) inhibited IPNV replication at very low concentrations. Similar efficacy was obtained with pyrazofurin, an OMP decarboxylase inhibitor. No inhibition was obtained with S-adenosylhomocysteine hydrolase inhibitors such as 5'-noraristeromycin, 6'-ß-fluoroaristeromycin and 3-deazaneplanocin A. Similar results were obtained with phosphonoformic acid (foscarnet). Compounds that produce some alteration in cellular membranes, such as brefeldin A and the triterpene sodium carbenoxolone, did not prove inhibitory to IPNV-induced plaque formation. We also evaluated whether the anti-IPNV agents affected cell viability and cellular DNA synthesis. From these studies pyrazofurin and EICAR emerged as the most promising drug candidates to be further evaluated in an *in vivo* setting.