SESSION 3

Preclinical Models and their Relevance for Clinical Cancer Prevention

S8. What is the Relevance of In-Vitro-Studies for Human Cancer Prevention?

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Metastatic cancer is the culmination of a multi-step carcinogenesis process, which may take several decades. This time provides opportunities for intervention. The development of novel strategies for human cancer prevention involves the identification of biological and pharmacological agents that can prevent, suppress, or delay the process of carcinogenesis. The ultimate test for the efficacy of a chemopreventive agent requires clinical trials to demonstrate reduction in cancer incidence. However, such trials necessitate that a large number of individuals be treated with chemopreventive agents for long time at very high cost. Therefore, it is important to optimize the process of identification and selection of new agents and populations at increased risk for developing cancer that express the target for these agents. The process of chemopreventive agent and molecular target identification, cellular pharmacology, and some mechanistic insights can be obtained using cells cultured in vitro. The development of techniques for cell immortalization by viral genes [e.g., Simian virus 40 (SV40) T antigen, adenovirus E1A and E1B, and human papillomavirus (HPV) E6 and E7], which inactivate the tumor suppressor genes p53 and Rb, or by non-viral approaches such as transfection of telomerase reverse transcriptase protein (TERT), alone or combined with CDK4 has generated cells with genotypic and phenotypic properties found in human premalignant cells. In addition, the exposure of such cells to human carcinogens (e.g., tobacco carcinogens) can lead to progression to more advanced premalignant and even malignant stages. Such in vitro cell systems can be valuable in screening agents for ability to inhibit transformation and for identification of effective combinations of agents that act synergistically. The use of in vitro systems has inherent deficiencies because of the separation from the original microenvironment and interactions with stroma, endothelial cells, and inflammatory cells. Some of these deficiencies can be corrected by growing the immortalized cells in 3-dimensional organotypic co-cultures. Other improvement of the in vitro systems are the generation of isogenic increasingly malignant cells by transfecting TERT-immortalized cells with mutant p53 or mutated K-ras or both and comparing their responses to chemopreventive agents using proteomics and genomics approaches followed by validation in specimens of premalignant tissues from human biopsies.