SESSION 4

S9. Genetically Altered Rodents and Human Tumor Cells as Preclinical Models for Prevention of Intestinal Cancers

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Single allele mutations in the adenomatous polyposis coli (APC) tumor suppressor gene have been detected in >90% of sporadic colon polyps and colon cancers in humans. Consequently, we have used *Min* (multiple intestinal neoplasia) mice, which have a stop codon mutation in codon 850 of the murine APC homolog and develop intestinal tumors, as a model of human intestinal carcinogenesis. This model has been useful in evaluating patterns of gene expression altered by mutant APC. Crossing these mice with knockouts has been useful in identifying modifiers of APC-dependent intestinal carcinogenesis. COX-1, COX-2 and NOS-2 have been identified as APC modifiers using this strategy. *Min* mice have been useful in evaluating intestinal cancer prevention strategies. Genetic evidence, obtained using knockout mice to implicate COX-1 and COX-2 in APC-dependent intestinal tumorigenesis, was corroborated by experiments indicating that APC-dependent intestinal carcinogenesis could be suppressed by treatment of COX-1/-2 wild-type mice with nonsteroidal antiinflammatory drugs (NSAIDS). Biochemical evidence, indicating that APC mutation was associated with increased expression of the polyamine biosynthetic enzyme ornithine decarboxylase (ODC), was corroborated by studies showing that the ODC inhibitor α-difluoromethylornithine (DFMO) suppressed intestinal tumorigenesis. Knockout studies have further demonstrated that the action of certain cancer prevention combinations, such as DFMO and piroxicam, work equally well in mice independent of p53. Genetic studies, using knockout mice, indicate that NOS2 acts to suppress APC-dependent intestinal carcinogenesis. This result suggests that arginine, or an NOS2-dependent arginine metabolic product, is a protective factor in (and consequently a possible therapeutic agent for prevention of) intestinal carcinogenesis. To investigate mechanisms of specific gene expression, we have used genetically altered human tumor cells. These cell culture models have been useful in understanding how APC mutations effect expression of genes, including COX-2, NOS2 and ODC. Cell culture studies are also useful in establishing the mode of action (e.g. anti-proliferative, apoptosis-inducing) of cancer prevention agents. Thus, genetically modified mice and genetically altered human tumor cells can be used to address a range of, albeit different, questions relevant to intestinal cancer prevention in humans. Both these preclinical models have been used to further establish the rationale for selected intestinal cancer prevention strategies.