

Lecture: gentechnology & animal experiments / transgenic animals

Epithelial cell lines for carcinogenesis and chemoprevention: an alternative to complement genetically engineered mouse models

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Background: Targeted organ site expression of oncogenes or repression of tumor suppressor genes have provided valuable *in vivo* animal models for genetically predisposed breast and colon cancer. Expression of clinically relevant genetic alterations in the target epithelial cells and quantifiable risk for carcinogenesis should provide an alternative approach to complement long term animal studies by refining and reducing *in vivo* experiments.

Models and Biomarkers: Mouse mammary epithelial cells stably transfected with Ras or c-myc oncogenes (MMEC-Ras, MMEC-Myc), and colon epithelial cells from Apc 1638N^{+/-} and Mlh1^{+/-}/1638N^{+/-} mutant mice (1638N COL, Mlh 1 /1638N COL) represented the cell culture models for breast and colon carcinogenesis, respectively. Cell cycle progression, cellular apoptosis and anchorage independent colony formation represented the quantitative surrogate end point biomarkers for the carcinogenic risk.

Study Outcome: Relative to the respective parental MMEC or COL cells, the MMEC-Ras, MMEC-myc, 1638N COL and Mlh1/1638N COL cells exhibited loss of homeostatic growth control (aberrant cell cycle progression, down-regulated apoptosis), and gain of anchorage independent growth *in vitro* and tumorigenesis *in vivo*. Treatment of the genetically altered mammary epithelial cells with pharmacologically achievable doses of mechanistically distinct synthetic or natural chemopreventive agents resulted in reversal of loss of homeostatic growth control and reduction of carcinogenic risk. In the genetically altered colon epithelial cells, mechanistically distinct agents in low dose combinations operated via additive/synergistic interactions to establish homeostatic growth control and reduce carcinogenic risk.

Conclusion: Quantifiable expression of the risk for carcinogenesis in these models and its reduction by chemopreventive agents validates a novel mechanism based approach to prioritize efficacious preventive/therapeutic interventions for long term *in vivo* studies on genetically engineered mouse models.

References

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