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GENETICS OF SKIN TUMOR PROMOTION SUSCEPTIBILITY

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Cancer susceptibility in the general population is a function of multiple, poorly penetrant modifier genes, each of which contributes to, but is not solely responsible for determining the likelihood that a particular type of cancer will develop after exposure to certain environmental carcinogenic agents. Genetic differences in susceptibility to two-stage skin carcinogenesis have been known for many years and the major contribution to susceptibility appears to be at the level of tumor promotion. Studies suggest that susceptibility to 12-O-tetradecanoylphorbol-13-acetate (TPA) skin tumor promotion is a multigenic trait. Loci that modify the susceptibility to TPA skin tumor promotion have been mapped to chromosomes 1, 2, 9, and 19 in genetic crosses of sensitive DBA/2 with relatively resistant C57BL/6 mice. One promotion susceptibility locus, *Psl1*, was mapped to an ~40 cM region of distal chromosome 9. Results from tumor studies using interval specific congenic mouse strains suggest that at least three genes that modify the response to TPA skin tumor promotion map within this region. These loci have been designated as *Psl1.1*, *Psl1.2*, and *Psl1.3*. Inheritance of the DBA/2 alleles of either *Psl1.1* or *Psl1.2* result in increased sensitivity to TPA while inheritance of the DBA/2 allele of *Psl1.3* results in decreased sensitivity. A large number of genes mapping to these regions have been associated with skin phenotypes or cancer development. Studies using subcongenic mouse strains and haplotype mapping are underway to further delimit the map locations of these loci. Furthermore, global gene expression analysis using cDNA microarrays have identified genes mapping to distal chromosome 9 that are differentially expressed in the epidermis of TPA-treated C57BL/6 vs DBA/2 mice, suggesting that these genes may be good candidates for TPA promotion susceptibility loci. Supported by NIEHS grant ES08355, NIEHS Center grant ES07784, and M.D. Anderson Cancer Center Core grant CA16672.