SESSION 7

Prevention of Skin and Brain Tumors

S23. New Perspectives on Melanoma Pathogenesis and Chemoprevention

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Epidemiologic observations attribute ultraviolet irradiation as etiologic in about 40-50% of cases. However, classical UV-mutations have not been documented in melanomas, either overall or in potentially relevant genes. Either UV is working indirectly or it is a surrogate for an as yet unidentified risk factor(s).

A series of experimental studies suggest that reactive oxygen species play a role in the pathogenesis of melanoma. Our initial data suggests that oxidation of melanin, which is normally an antioxidant, and its "transformation" to a pro-oxidant is an essential early feature of melanomagenesis. Based on this observation, we propose that:

1. Either melanin oxidation is a primary event or a genetic abnormality leading to this condition is fundamental (i.e. mutation of NADPH oxidase or of a melanosomal structural protein);
2. Oxidized melanin provides a unique pathway for the development of drugs targeted to the putative quinone–imine(a chelator) in oxidized melanin;
3. Activation of the multifunctional protein, apurinic-apyrimidimic endonuclease/redox-effector factor-1 provides a key target for intervention;
4. Oxidation of mitochondrial DNA leads to unique respiratory chain mutations that convey a unique drug resistance phenotype; and
5. Heavy metals and similar components need to be re-examined as potential co-factors in melanoma pathogenesis.

These leads provide new and varied opportunities to develop chemoprevention for human melanoma.