Melanoma Biology and Progression

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A group of 25 investigators met on November 6–8, 2000 in Bethesda, MD for the purpose of accelerating progress in understanding the biological events in melanoma as they relate to etiology, immune response, and progression. The format of the meeting was the presentation of brief reports that focused on concepts rather than specifics, with extensive discussion periods to identify the issues and barriers hindering progress in the field. This report summarizes the findings of the meeting, highlighting the recent advances in understanding melanoma development and progression and addressing opportunities for better diagnosis, prognosis, and therapy. Several specific recommendations are made to strengthen the field and advance knowledge and progress.

The meeting started with overviews on melanocytes and melanoma. This session was chaired by Meenhard Herlyn (The Wistar Institute, Philadelphia, PA). Dorothy Bennett (St. George’s Hospital, London, United Kingdom) summarized the current information on melanocyte development, homeostasis in the adult skin, and the role for the INK4A tumor suppressor gene in senescence. Margaret Tucker (National Cancer Institute, Bethesda, MD) presented epidemiological data of genetic and environmental causes of melanoma. The p16 gene alterations are important in the development of familial melanoma but apparently not for sporadic melanoma. Main risk factors for melanoma are the total number of nevi, number of dysplastic nevi, color of hair, skin, and eyes, and sun exposure during childhood. David Elder (University of Pennsylvania, Philadelphia, PA) outlined the different stages of tumor progression in melanoma, particularly the transition from a biologically early stage of primary melanoma of the radial growth phase, which has no propensity to metastasize, to the advanced primary melanoma of the vertical growth phase, which is associated with increased risk for metastasis. Global gene expression profiling of melanoma, outlined by Jeffrey Trent (National Human Genome Research Institute, Bethesda, MD) promises to help not only melanoma diagnosis but also understanding the biological events during progression.

The session on melanoma models was chaired by Mary Hendrix (University of Iowa, Iowa City, IO). It dealt with both human and mouse models. Human skin grafted to immunodeficient mice, presented by Meenhard Herlyn, provides an orthotopic environment for UV-induced melanomagenesis, in which mice, the Mexicanoopossum, or Xiphophorus hybrid fish are used as melanoma models. Suzie Chen (University of Iowa, Iowa City, IO) outlined how melanoma cells signal after UV or ionizing irradiation and how knowledge of the signaling pathways can help in developing new strategies for overcoming the notorious radiation and chemoresistance of melanoma cells. In contrast to normal melanocytes, melanoma cells produce a variety of cytokines and growth factors for autocrine and paracrine stimulation. Ruth Halaban (Mount Sinai School of Medicine, New York, NY) outlined how melanoma cells signal after UV or ionizing irradiation and how knowledge of the signaling pathways can help in developing new strategies for overcoming the notorious radiation and chemoresistance of melanoma cells. In contrast to normal melanocytes, melanoma cells produce a variety of cytokines and growth factors for autocrine and paracrine stimulation. Ruth Halaban listed the major receptor tyrosine kinases that are active in the melanocyte system, including those for basic fibroblast growth factor, hepatocyte growth factor, stem cell factor, and insulin-like growth factor signaling. Cell cycle dysregulation appears to play a major role in melanoma, particularly through the RB and cyclin D pathways.

Melanoma cells are highly immunogenic in patients, eliciting both humoral and cell-mediated immune responses. In fact, melanoma has been the prime model among all of human cancers for studying the immune response against cancer cells because of the relative ease of culturing normal and malignant melanocytes. Soldano Ferrone (Roswell Park Cancer Institute, Buffalo, NY) pointed to the potential dysregulation of the cell-mediated immune response in melanoma patients, which may be attributable to down-regulation or loss of HLA class I molecules. The latter abnormalities are caused by mutations in the genes encoding the HLA class I subunits and/or by defects in the
components of the antigen-processing machinery. Francesco Marincola (National Cancer Institute, Bethesda, MD) analyzed the phenotypes of melanoma cells by global gene expression before and after cytokine therapy to develop better prognostic criteria for cytokine and vaccine therapies. New antigens are currently being identified that are suitable for eliciting both humoral and cell-mediated immune responses. The strategies used in these studies that may lead to the development of new vaccine targets were summarized by Yao-Tseng Chen (Cornell University, New York, NY) and Dorothee Herlyn (The Wistar Institute, Philadelphia, PA). Genes associated with pigmenta-
tion appear particularly immunogenic. Peptides derived from pig-
ment-related and -unrelated proteins are being used for active immu-
nization, either together with adjuvants or coupled to autologous
dendritic cells that are propagated in vitro. Antigen-specific T cells
from melanoma patients can also be expanded in vitro and then
reinfused to the same patients in an adoptive immunotherapy strategy,
as demonstrated by Cassian Yee (Fred Hutchinson Cancer Center,
Seattle, WA). It became obvious from this session that rapid progress
is being made in identifying new biological and immunological tar-
gets for melanoma therapy. However, each strategy has its own
challenges to overcome. New in vivo imaging techniques, as demon-
strated by Dorothea Becker (University of Pittsburgh, Pittsburgh, PA),
should help in validating the biological significance of selected
targets.

The final session on melanoma progression and stroma was chaired
by David Fisher (Dana-Farber Cancer Institute, Boston, MA). It dealt
with tumor matrix, motility and invasion, and transcriptional regu-
lation of growth. Peter Brooks (New York University, New York, NY)
has identified epitopes in collagen that are potential targets for therapy
because only melanoma-derived enzymes expose them. Matrix met-
alloproteinases, the extracellular matrix, and adhesion receptors form
functional units that are critical for tumor progression (Yves DeClerk,
University of California, Los Angeles, CA). Melanoma cells may also
develop properties that resemble those of endothelial cells. Mary
Hendrix and coworkers have identified channels that are devoid of
endothelial cells but still allow blood flow. David Fisher outlined
the major transcription factor systems. For melanocyte development, the
MITF transcription factor appears most critical. In melanoma, there
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