Driving in the melanoma landscape

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Abstract: The melanoma landscape is rapidly evolving. The melanoma oncologists have now the first successful targets for therapy that have a genetic base – albeit in rare forms of the malignancy. Once melanoma becomes part of the Cancer Genome Atlas consortium, a comprehensive map of genetic changes will be established to point the field to true drivers of the disease that will become new targets for therapy. The same abnormalities will also serve as biomarkers for diagnosis, prognosis and therapy follow-up. Melanomas as a group are heterogeneous as are tumor cells within one lesion. New strategies will move towards individualized therapies and combination therapies to target all cells within a tumor.

Key words: melanoma – stem cells – oncogenes – targeted therapy

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For long-term planning, in both government and industry, experts may perform a SWOT analysis, which stands for strength, weaknesses, opportunities and threats. Such analyses provide a valuable current-state assessment, on which one builds strategic plans for the future. Three years ago, a group of over 40 melanoma investigators developed a consensus ‘Roadmap for Melanoma Research’, which continues to guide our discussions (1). We started with a SWOT analysis of the current state of the melanoma landscape to better formulate what direction the field should move in. This initial analysis is outdated in the science areas but not with regard to the general needs of the field. Have we gotten stronger? The science has progressed significantly, however, lack of funding, particularly in the US, has prevented us from taking full advantage of this progress. Like in the previous decade, progress in basic science is outpacing that in the clinics and thus our challenge for the future is to better connect the laboratory with the clinics. Translational research is difficult to materialize, and the obstacles are formidable. We need to train a new generation of researchers who can seamlessly switch between clinical and basic research languages and who will drive the field by bringing the laboratory closer to the clinics. In this brief overview, we will focus mostly on the opportunities for the melanoma landscape and where we can expect the most progress in the next few years.

The drivers

Melanoma development, and likely also progression, depends on genetic alterations that drive the cells to grow, migrate, invade and survive in a ‘hostile’ world of hypoxia, loss of attachment and cell death triggers both natural and induced by treatment regimens. Melanomas are ‘addicted’ to genetic oncogenes and tumor suppressor genes that are genetically altered. We can drive progression by stimulating the environment for the production of growth factors, but the lesions will collapse if there are no constitutive drivers. Which ones are important? Members of the MAPK pathway, the central proliferation pathway, are important, with most frequent mutations in BRAF, NRAS and c-kit. If we combine mutations in BRAF (50–60%), NRAS (15%) and c-kit (2–4%), we end up with approximately 70% of all cases that carry a mutation in one of these genes, which is a remarkably high frequency and apparently very important for the tumor. Because nevi already carry the mutations, at least for BRAF and also some for NRAS, we need to consider additional mutations that are drivers of melanoma. We can only speculate on the additional genes. Melanomas are very aneuploid and carry hundreds of mutations. Unless we perform genome-wide sequencing, we will not find the correct answers on the hierarchy of gene mutations for a long time. Because melanomas are also very heterogeneous, we cannot get the answers from sequencing only a few specimens. The plans for such an undertaking are in place and the consensus among the experts of major sequencing centres is that 500 specimens are needed to cover all melanoma sub-types in sufficient numbers. What are the obstacles? At this time, most of the technologies are in place and it would take an estimated 5 years. What is the price tag? The costs for sequencing one genome are coming down rapidly. Two years ago, it was $1–2 million, currently it is down 10 fold and it is expected that the price may decrease...