

Translating Melanoma Biology to Melanoma Therapy

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The therapy of advanced unresectable melanoma has made little progress over the past 20-30 years. Most of the effort aimed at new treatments has centered on enhancing either an innate or adaptive arm of the immune response. While the science of tumor immunology has progressed rapidly, this has yet to translate into better therapy. Even though IFN- α has been approved as an adjuvant treatment for high risk regional melanoma and Interleukin-2 is approved for therapy of advanced disease, these are woefully inadequate treatments. These treatments can be quite toxic and are generally limited to patients with very good organ function. Additionally, chemotherapy has always had very limited success in melanoma and there is no convincing evidence of improved survival due to treatment. Recently, there has been an exciting flurry of work to define potential targets for new therapeutic agents in melanoma, since empiric therapeutic approaches have led to little if any progress in the treatment of this disease. These efforts have invigorated the melanoma research field. Melanoma should no longer be perceived as a single disease process with a similar response to a single intervention, based on abundant data from numerous laboratories studying life and death pathways in melanoma. Indeed, melanoma is characterized by multiple genetic mutations, gene amplifications, gene deletions, and constitutive activation of signaling pathways, all of which may occur independently or as a consequence of events in a single tumor. It will be vital to develop preclinical models that can better predict the effects of therapy in the melanoma patient. We also now know that melanoma comes in a broad spectrum of biologic behaviors and no one melanoma is identical to the next, hence the difficulty in finding the “magic bullet” for one-size-fits-all therapy. The question is how are we going to use this biologic diversity to our advantage and move the therapy forward? It will take a careful analysis of each tumor we treat and the impact of the specific targeted agent on its intended pathway, as well as, its effect on off-target pathways. Hopefully, we can develop a predictive model to guide more rationale therapeutic decisions.

Agents targeting many of the signaling pathways affected by and critical to cancer are in late preclinical, phase I, or early phase II evaluation in numerous adult cancers including melanoma. With this new array of agents and trials, it will be critical to gain vital information explaining the underlying causes of treatment failures. In many ways, this may be even more important than understanding therapeutic successes. However, a potential flaw with many of the ongoing clinical studies is that melanoma patients are enrolled without routinely being evaluated for the presence of the specific target or for the characteristic molecular phenotype associated with the desired drug (anti-tumor) effect. Frequently, the molecular phenotype of the melanoma under treatment is largely unknown. While a significant percentage of malignant melanoma patients have constitutive I κ B kinase activation, NRAS or BRAF mutations, or c-kit mutations, these characteristics are variable. Other mutations or dysregulated pathways may be of importance, such as PTEN loss and Akt activation. The matter is not simplified by the

use of melanoma cell line models in the laboratory in an effort to discern the biology of the disease. As cell lines are established in the laboratories and expanded in almost infinite numbers, they are devoid of the influences of their “natural” environment (e.g. cytokines, hormones) and new mutations and molecular changes are introduced, which may or may not be true in the tumor microenvironment of human cancers. Thus, the first step towards finding more effective therapeutics is to base our clinical trials on better pre-clinical models. explants

We and others in the field have embarked on a strategy based on the idea of using freshly biopsied melanoma tumor implants in mouse models to ensure minimal manipulation of the tumor in the laboratory setting. Prior to implantation, one could molecularly phenotype the tumors in order to help define the most appropriate targeted treatment option. Once the xenograft is established, the mice will then be exposed to the agents of interest and effect on tumors will be studied both at a macroscopic and microscopic level. Then based upon the molecular phenotype of each of the melanomas transplanted and their response to the specific targeted therapy (as determined by growth inhibition and apoptosis), one could derive a model for predicting the tumor phenotype most likely to clinically respond in treatment. The final test of the model will be its utilization in selecting how melanoma patients will be assigned treatments in the clinic. Prior animal models have been very poor predictors of clinical efficacy, possibly due to lack of molecular compatibility of the xenograft tumors to the clinical tumors. To fully correlate the mouse xenograft response to therapeutic agents to that of the human patient, we need to compare the tumor response in the patient to that of the human tumor xenograft in the mouse. While mouse and human response to tumor may be very similar, they may also be very different with the T cell immune system gravely compromised in nude mice. However, the hope is that the *in vivo* xenografts will allow for correlation between tumor regression and successful targeting of the specific pathway by the inhibitor. The mouse model ideally could be performed in parallel with the patient’s treatment. By characterizing the molecular signature of melanoma implants and then determining whether there is a correlation between specific molecular alterations and response to targeted therapy in the mouse melanoma xenografts, we can determine whether it will be useful to perform molecular profiling on tumor biopsies and treat patients based upon this diagnostic information.

Melanoma more so than other cancers is an ever changing disease involving frequent alterations and high mutation rates, hence demanding a molecular perspective to treatment in order to further improve outcomes. The challenge is to bring the clinical and basic sciences together, and thereby, broaden and improve the connection between molecular features of cancer and cancer therapy. The concept of molecular phenotyping will be fruitless, if the interplay between the bench and the bed is few and far between. The coalition is vital and mandatory in the war against this deadly disease, because without it victory will be just as transient as the responses currently observed in clinic.