

CANCER

Focus Issue: Cancer—Beyond tumor genetics to protein landscapes

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The proteins that regulate cell proliferation, metastatic potential, survival in circulation, and immune evasion represent most of the targets for therapeutic intervention in cancer. Furthermore, genomic profiling of just the cancer cells leaves critical information about the tumor microenvironment in the dark. The articles highlighted in this Focus Issue describe efforts to translate genomic data into knowledge of aberrant signaling that can be therapeutically targeted and strategies to explore not only the changes that occur in the protein landscape of the tumors but also in the protein profiles of the tumor microenvironment.

The Cancer Moonshot initiative aims to bring more effective therapies and diagnostic tools to the clinic through increased coordination of research resources. Rapid and easy genetic sequencing technology has created an accessible way to screen tumors for potentially initiating or driving mutations. Many mutations in the genes encoding signaling proteins are common to various tumor types, such as activating mutations in the kinase BRAF or the guanosine triphosphatase (GTPase) RAS or loss-of-function mutations in the tumor suppressors PTEN or p53. However, ultimately, it is the function of proteins that drive tumor growth, drug resistance, and metastasis, and it is the proteins that are most often therapeutically targetable. In this special issue of *Science Signaling*, the Review by Liu *et al.* describes the signaling pathway-level effects of genetic mutations in various pediatric brain tumors that may be therapeutically targeted in patients. Reviews by Obacz *et al.* and Mészáros *et al.* highlight the detailed mechanisms and therapeutic potential of targeting proteostasis-related pathways in cancer cells, particularly how inhibiting the unfolded stress response might inhibit the growth of glioblastoma. The Review by Mészáros *et al.* focuses on how dysfunction of ubiquitin-mediated protein degradation contributes to cancer. This Editorial Guide highlights research published in the past 6 months in *Science Signaling* with an emphasis on those studies that examined how changes in the protein landscape contribute to tumor development, growth, and metastasis.

Research must move beyond tumor genomic profiling to understand how a tumor is regulated, how its microenvironment is regulated, and, critically, how the tumor and cells in its microenvironment communicate. Techniques such as cytometry by time of flight (CyTOF)

and multiparametric antigen analysis enable simultaneous evaluation of tumor heterogeneity and the microenvironment. Simmons *et al.* performed CyTOF analysis on formalin-fixed, paraffin-embedded tissue to identify changes in signaling activity within single cells of colon tumors compared with those from normal tissue. Their analysis revealed cellular heterogeneity at the protein level, as well as potentially ways to tumor cells within tissue that has a complex architecture, such as the colon. Ostalecki and Lee *et al.* performed systematic tissue antigen analysis to identify changes in protein abundance, localization, and activity that drive less invasive melanoma cells with a common protumorigenic mutational landscape (BRAF^{V600E} with PTEN deletion) to aggressive invasive melanoma. Their findings revealed a cell contact-mediated mode of communication by which melanoma cells instruct surrounding keratinocytes to increase the release of tumor-promoting growth factors. The tumor cells extended processes that transferred the metalloproteinase ADAM10 that had been activated in endosome through an interaction between a peptidase. This endosomal ADAM10 activation in the cells was an early and possibly initiating event in the malignant transformation of melanocytes. The activation of ADAM10 and the resulting protein landscape changes in keratinocytes were not accompanied by genomic- or transcript-level changes, so these tumor-promoting events would not have been detected through genomic analyses.

Protein-protein interactions are critical to protein (and ultimately cellular) function. Alterations in these interactions—which cannot be detected through genomic methods—can halt, enhance, or change the biological output of a signal. Numerous studies published in *Science Signaling* (most recently Halasz *et al.* and Zhang *et al.*)

have created protein-level network models to predict therapeutic efficacy and resistance mechanisms in various tumor types. Caromile *et al.* examined the metastatic prostate cancer marker prostate-specific membrane antigen (PSMA) and found that its presence at the cell surface disrupts the interaction between a growth factor receptor [insulin-like growth factor 1 receptor (IGF1-R)] and a scaffolding protein, an event that shifts the balance of signal transduction from a cell proliferation-associated pathway to a more aggressive, cell survival-associated pathway. This (i) explains why PSMA abundance, which was not the result of a mutation, is a marker for advanced disease; (ii) suggests using clinically approved drugs to target the more aggressive pathway, which did not contain activating mutations or increased genetic expression of its components; and (iii) indicates a new avenue for therapeutic intervention through disrupting the interaction between PSMA and the scaffold for patients with PSMA-positive cancer. Gemmill *et al.* identified an isoform-specific difference in protein interactions, the inability of an isoform of neuropilin-2, NRP2b, to interact with PTEN, as enhancing the responsiveness and motility of lung cancer cells exposed to the growth factor TGF- β . Gamell *et al.* also found that a reduction in a protein interaction enhanced the progression through the cell cycle and thus contributed to cancer. In this example, decreased abundance (not caused by genetic mutation or deletion in patients) of the E3 ubiquitin ligase E6AP promotes the growth of lung tumors through the loss of its inhibitory interaction with a transcription factor that stimulates the expression of a cell cycling gene *CDC6*. The increase in *CDC6* resulted in suppression of the expression of the gene encoding the tumor suppressor p16. In other tumors, decreased expression of *p16/ARF* locus is explained by promoter methylation, but this event does not occur in all lung cancer patients with reduced p16. Thus, a protein-directed

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analysis explained a previously puzzling expression profile and uncovered a potential therapeutic avenue. Shi *et al.* looked at protein abundance patterns in various cell types and found that the abundance of adaptor proteins—not the receptor—is rate-limiting in dictating the signaling intensity and biological output of the epidermal growth factor receptor (EGFR) pathway. This suggests that targeting adaptors rather than the receptor may be more effective at suppressing growth-promoting signals in tumor cells. Croucher *et al.* applied a method that detected dimer-specific conformations of proteins to breast cancer cells. They found that distinct dimer formation between members of the EGFR family is associated with distinct interaction networks of adaptors and other proteins and consequently produces different transcriptional profiles and cellular behaviors.

Protein-protein interactions are also regulated by posttranslational modifications, mediated through changes in conformation or subcellular localization of the modified protein. Investigating metastatic ovarian cancer, Antony *et al.* identified protein network changes associated with cell motility that were caused by increased abundance of the receptor tyrosine kinase AXL. Brand *et al.* found that the phosphorylation of the cytoplasmic tail of EGFR was stimulated by AXL activation. This phosphorylated EGFR translocated to the nucleus and stimulated genes encoding proteins that promote cell motility. However, neither AXL nor EGFR has alterations at the gene or transcript level, and, like protein networks, neither phosphorylation nor subcellular localization is detectable through genomic analyses, so this underlying mechanism of tumor metastasis would not have been detected with a genetic profile of a patient's tumor. Various posttranslational modifications regulate protein stability as well as activity. Nihira *et al.* reveal how acetylation of MDM2 in specific residues alters its conformation and subsequent protein-protein interactions that dictate whether MDM2 ubiquitinates itself or its substrate p53, marking one or the other for degradation. Thus, ultimately, these compound modifications regulate whether stress (or chemotherapy or other targeted therapy) triggers cell death or adaptation to the drug.

Genomic and transcriptomic profiling does have value and can be an effective starting point for investigating the resulting aberrant protein profile and functional consequences. Ruggiero *et al.* started from the altered transcriptional profile of adrenocortical carcinoma to discover a key transcriptional regulatory pathway that resulted in the increased expres-

sion of the gene encoding VAV2 and thus increased abundance and activity of this cytoskeletal regulatory protein that promotes cell motility and metastasis of the cancer. Thus, knowing whether a gene contains mutations or exhibits altered expression is only the beginning of unraveling the molecular details required to understand a tumor and develop and apply effective treatment strategies. Researchers must examine the function, modification, localization, and interaction networks of the encoded proteins in tumor cells and cells of the tumor microenvironment. The articles highlighted here exemplify just some of the cancer research published in *Science Signaling*, and, like some of the Cancer Moonshot initiatives, these studies reveal basic aspects of cancer biology that can be leveraged for patient stratification and therapeutic development.

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