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Morphoproteomics: Bringing Personalized Medicine to the Cancer Patient

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We are now in an era of molecular pathology which presents pathologists with the opportunity to study the underlying pathogenesis of lesions at the molecular level, in addition to making a pathological diagnosis based on morphology. The ultimate goal of such integration would be to provide insight into the biology of the disease process contained in a patient's specimen so that therapies could be customized for that individual patient. Among the methodologies for molecular study, there is a relatively new approach called "morphoproteomics" which is unique to anatomic pathology because it combines morphology with proteomic analysis [1].

By way of background, there are varied methodologies used in the field of proteomics, including gel-free, label-free proteomics, quantitative proteomics, phosphoproteomics, protein extraction from formalin-fixed, paraffin-embedded tissue sections (FFPE) proteomics, laser capture microdissection proteomics, and targeted tissue proteomics. Morphoproteomics is performed on FFPE sections and uses immunohistochemical probes to help characterize the molecular circuitries that exist both within the tumor cells and the surrounding tissues in the tumoral microenvironment. Moreover, morphoproteomics can assess the impact of such molecular circuitry in a tumor by visualizing the state of activation of key protein analytes, noting their subcellular translocation, phosphorylation and correlative expressions with other upstream activators or downstream effectors and their relative level of expression or overexpression vis-à-vis their non-neoplastic counterparts [2,3].

Molecular tumor profiling using morphoproteomic analysis allows one to consider the following categories of protein analytes in a tumor that have therapeutic implications: *Upstream signal transducers* (e.g., epidermal growth factor receptor [EGFRvIII/EGFR], HER-2/neu, c-Met [phosphorylated on tyrosine 1234/1235], protein kinase C-alpha, and phospholipase D1 and D2); *Pathways of convergence of upstream signaling* (e.g., Ras/Raf kinase /extracellular signal –regulated kinase [ERK] using ERK 1 /2 phosphorylated on threonine 202/tyrosine 204; the mTORC1 and mTORC2 using plasmalemmal expression of mammalian target of rapamycin [mTOR] phosphorylated on serine 2448 along with concomitant nuclear p-p70S6K [Thr 389] as evidence of mTORC1 and nuclear p-mTOR [Ser 2448] along with nuclear p-Akt [Ser 473] its downstream effector as evidence of mTORC2); *Cell cycle-related analytes* (e.g., Ki-67 [G1, S, G2 and M phases], S-phase kinase-associated protein [Skp]2, cyclin –dependent kinase activators and facilitators [cyclin D1, p53 as mutant form, nuclear beta-catenin], cyclin-dependent kinase inhibitors [p27Kip1, p16INK4a], repair enzymes [Topoisomerase II alpha] and mitotic index); *Tumorigenic/angiogenic/chemoradioresistance/prosurvival factors* (e.g., signal transducer and activator of transcription [STAT] pathway in the form of p-STAT3 [Tyr 705], a downstream effector of Src-STAT and JAK/STAT signaling; nuclear factor kappa B [NF-kappaB], evidenced by nuclear translocation of p-NF-kappaBp65 [Ser 536]; anti-apoptotic protein, Bcl-2; multidrug resistant efflux pump, P-glycoprotein; fatty acid synthase[FASN]; heat shock protein chaperone system, Hsp90; COX-2;vascular endothelial growth factor signaling, VEGF-A); *Stemness/epithelial-mesenchymal transition/sonic hedgehog pathway indicators* (e.g., neural precursor lineage, CD133 and nestin; CD44; E-cadherin and vimentin; nuclear glioma-associated oncogene protein [Gli]2; and non-canonical TGF-beta [Smad3} signaling suspected in the form of nuclear Gli2 and stromal alpha-smooth muscle actin expressions and markers in evidence of epithelial-mesenchymal transition); *Potential differentiation-facilitating/proapoptotic/oncostatic markers* (e.g., melatonin receptor 1a [MTR-1A]; peroxisome proliferato- activated receptor [PPAR] gamma; tumor necrosis factor-related apoptosis-inducing ligand [TRAIL]-receptor 1[DR4]; *Immune surveillance factors in the microenvironment* (e.g., assessment of the numbers of intratumoral cytotoxic lymphocytes [CD8+ and CD56+/CD3-] lymphocytes versus the numbers of T-regulatory/suppressor lymphocytes [nuclear FoxP3+] lymphocytes; and *Chemotherapy/anti-angiogenic -facilitating proteins and chemoresistance signatures* (e.g., secreted protein acidic and rich in cysteine [SPARC; osteonectin] expression in tumor cells, stromal cells and endothelium as a potential guide to the selection of nab-paclitaxel and excision repair cross complementation group 1 [ERCC1] and CD44 expressions as a guide to the consideration of platinum agents).

The selection of the immunohistochemical probes for a given case is guided in part by the tumoral phenotype and the histopathology by bright-field microscopy, in part by the previous therapies, in part by computer-assisted mining of the National Library of Medicine's MEDLINE data base, in part on the results of imaging and scintigraphic studies and in part on the therapeutic considerations of our clinical, oncologic colleagues.The therapeutic implications and considerations also take into account both the ever increasing number of agents in the therapeutic arsenal to address the biology of the patient's tumor and the concomitant genomic studies on a given tumor (e.g., activating mutation of the *EGFR, K-RAS* and *BRAF genes* and the methylation status of the *MGMT* gene). Such therapeutic agents currently available include signal transduction pathway inhibitors, apoptosis-inducing agents, prosurvival pathway inhibitors, differentiating agents, anti-angiogenic agents, epithelial-mesenchymal transition inhibitors, anti-tumoral stem cell agents, oncostatic agents, and immune modulating agents. Finally, the application of morphoproteomics to sequential biopsies of a metastatic and recurrent tumor can give insight into the adaptive responses of the tumor, its resistance signatures and opportunities for new therapeutic strategies.

Since its initial application in clinic in 2007 at the University of

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Texas, department of pathology and laboratory medicine, the cases of morphoproteomics have been increased exponentially over the years. In 2007, there were only 4 cases; by year of 2010, there were 97 cases. The cases being analyzed include neuroblastoma, colon cancer, hepatocellular carcinoma, head and neck cancers, lung cancer (both small and non-small cell), renal cell carcinoma, ovarian carcinoma, breast cancer, uterine cancer, glioblastoma, osteosarcoma, medulloblastoma, prostate cancer, leiomyosarcoma and rhabdomyosarcoma, and occasionally hematopoietic tumors. Most of times, the oncologists request morphoproteomics analyze when the tumor does not respond to conventional chemotherapy, or the disease is at the advanced stage and widely speeded. The report of the morphoproteomics analysis usually includes the following parts: first it starts with a table that lists all the markers, the quantitative expression of each marker and the cellular location of the expression; second, followed by detailed interpretation of the each marker, which is grouped by cell cycle related analytes, upstream signal transducer, downstream effectors, antiapoptocit/tumorigenic/angiogenic/chemoresistance factors, stem cell markers and tumor infiltrating lymphocyte markers; third, an algorithm of recommendations for treatment based on the morphoproteomics data. Oncologists find the analysis very helpful and some cases have significant therapeutic improvement after following the recommendations.

In summary, morphoproteomics enables the pathologist to add another dimension to the understanding of the biology of a patient's tumor and the opportunity to contribute to therapeutic intervention that is customized for that individual patient (personalized medicine). Moreover, morphoproteomics will enable our clinical colleagues to choose the maintenance therapies that can be applied to keep those tumor cells that have developed stemness and epithelial-mesenchymal transition status in a quiescent state, to facilitate their differentiation into a more benign form, to promote more effective immune surveillance and to alter the microenvironment so that epigenetic factors that might promote their expansion are minimized and the risk of recurrent disease is reduced.

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