Editorial

Pediatric oncology: Looking ahead

Over the past ten to fifteen years, a silent revolution in pediatric surgical oncology has been altering the clinical practice, and in the near future, it will alter the way we diagnose and treat pediatric tumors.

Ever since van Leuwenhoek has looked through his single lens microscope in the late seventeenth century and noted “animalcules” in a drop of water, this form has been regarded as a surrogate for function.[1] Since 1680, this view has prevailed and has formed the basis for anatomical pathology and that for our current classification of neoplastic diseases.

Clinicians are anxious to be able to predict the behavior of a tumor within a given host, and it has become abundantly clear that form and function are largely independent properties of neoplastic cells. In clinical practice, it is not unusual to see tumors that look identical under a pathologist’s microscope demonstrating wildly different behavior patterns in patients. Classically, neuroblastomas that spontaneously recede look identical to neuroblastomas that progress, notwithstanding Shimada’s histological refinements.[2] The cells of papillary thyroid malignancies can look so normal that the concept of the “lateral aberrant thyroid” gained credence to explain cervical lymph node metastases.[3] Neonatal fibrosarcomas that “look” malignant behave benignly and may be more closely related to mesoblastic nephroma than to other sarcomas.[4] There are innumerable examples of the folly of inferring behavior from form or anatomy.

Nonetheless, pathologists have been attempting to predict cellular behavior from a more detailed study of cellular anatomy. As for three centuries, the light microscope has been the only instrument available for the study of cells it is perhaps not surprising that our entire classification of tumors is based upon cellular structure rather than anything more rational. We even talk about things “looking” malignant despite the obvious fact that malignancy is a behavioral characteristic not an appearance. We have, in essence, been trying to judge books by their covers; somewhat like attempting to predict the performance of a group of medical students based upon some anatomical feature such as the length of their hair. It has long been apparent that this approach is limited, if not ridiculous, but until the development of cell culture techniques and the completion of the human genome project, there was little alternative.

It is clear that within any given cellular appearance there are a multitude of potential cellular behavior patterns and, particularly in pediatric solid tumors that consist of multiple cell types, the prediction of biological behavior is complex.

Pathologists have successfully refined nosology based on histological features that are known to be associated with poor clinical outcomes, such as the identification of unfavorable histological features in nephroblastoma[5] or neuroblastoma, but these histological features are only a manifestation of the tumors’ genetically-determined behavior and are, of themselves, of little value.[6]

It makes much more sense to look directly at the genome of the tumor cell.

Currently, this is a standard practice in many centers to stratify risk, for example in neuroblastoma, the risk is stratified according to genomic aberrations such as DNA ploidy, nMYC amplification, and chromosomal gains and losses, in addition to host factors such as age.[7] Pathologists now routinely use markers for genetically determined surface antigens in order to classify tumors. However, so far, classification has been useful since it predicts behavior. Currently, genetic characteristics such as HER 2 receptor status and hormone receptor profiles in breast cancer have become an essential part of diagnosis and treatment planning.[8] Each newly recognized surface antigen is another potential target for a monoclonal antibody. This philosophy will spill over into the sphere of pediatric malignancies, and each new genetic aberration will entrain new treatment targets and strategies.

It is now clear that there are certain characteristics of the malignant cell, genetically-determined characteristics, which in a given host will predict behavior. Treatment is determined not only by the crude parameters of stage and histological appearance that governed the decisions of previous generations, but by an assessment of risk that incorporates host factors as well as these genomic aberrations within the tumor cell.[9] In monoclonal tumors such as leukemias, risk assessment can be fairly precise. However, pediatric solid tumors such as nephroblastoma are typified by a polyclonal expansion of malignant cells each of which will have different genomic aberrations, and therefore, different behavior patterns including metastatic potential,
angiogenic capacity, and susceptibility to different chemotherapeutic agents.\[10\]

This recognition of genomic injuries will surely develop further such that today’s students will, before their professional careers are done, cease to talk about “neuroblastoma” but will define the disease as a neuroblastic tumor with a specific and well-defined genomic profile. These genomic characteristics will predict cellular behavior and hence risk. The genomic aberration will define potential treatment targets, and along with general factors within the host, these will determine outcome. It is anticipated that the results of such a structured approach will be better than guessing.

The molecular biologist is set to become an essential member of the diagnostic and therapeutic team; as important as the histopathologist has been in the past.

Viva la revolucion!!!

REFERENCES


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