Digital Spatial Profiling

Combing modern molecular profiling with established pathology.

Current methods in pathology rely on established techniques that have changed very little in the past 50 years. We have a lot of experience using H&E staining to interpret the morphology of cells and tissues. What we're missing, though, is an opportunity to integrate information from the other ends of the scientific spectrum: subcellular activity at the molecular level and 3D context of the whole tissue environment.

At the molecular level, we can look at the leading edge of a tumor and its interactions with the surrounding immune cells and native tissue. We can assess if and how the situation at the leading edge is different from what is observed at the center of the tumor. Using a combination of markers we can then identify a set of traits, or molecular profile, that is characteristic of active tumor proliferation and immune reaction. Armed with this knowledge we can examine other sites and determine if they are transitioning to a more active, and possibly more aggressive, state. The more markers we have in the profile, the more accurate and reliable the profile will be. In a perfect world we would image 38 different markers at the same time. Based on the technology available today we would be lucky to have six.

We are using light sheet fluorescence microscopy to image the tissues so that we can collect the spatial information that is lost using serial sectioning and flow cytometry. But the tradeoff is that we are limited to the number of markers we look at in one experiment. In one immunohistochemistry (IHC) stain-based project, we screened 33 proteins, but we had to winnow it down to the top three for practical reasons. This meant we had to make compromises and omit a lot of potential candidates so as a result our profile is far from complete. What immediately struck me as being so exciting about the Digital Spatial Profiling (DSP) technology is that I can visualize an order of magnitude more proteins and then use the same tissue for serial sectioning and H&E. It combines the best of both worlds from modern molecular biology and established pathology.

Dr Nick Reder, MD, MPH currently works at the Department of Pathology at the University of Washington in Seattle. Part of his time is spent in collaboration with mechanical engineers at UW developing ways to apply light sheet microscopy to improve existing pathology practices. Here he shares his thoughts on the future of the field.

For my own research, I am looking forward to applying DSP to create a molecular profile for prostate cancer. Patients who have their prostate removed are monitored for 10-15 years afterwards. The cancer can be slow to grow back, so regular blood tests of PSA levels are used as an indicator of cancer activity. If the prostate cancer recurs not only can we examine their current tissue, we can go back to their original sample. Furthermore, we can compare the molecular profiles of patients who develop cancer again to those patients who do not and see how they differed during the original diagnosis. Imagine if we can find a profile that represents a slow growing cancer that will not have a recurrence? We can tailor the patient's treatment to deal with a less aggressive type cancer and possibly avoid surgery altogether.

As pathologists, we are being asked to do more with less. 30-40 years ago, pathologists would often get large biopsy samples just for H&E staining. Now biopsy samples are smaller but the list of expected tests is longer. For example, a suspected breast cancer sample would be examined by H&E, probably four IHC stains, and NCCN Clinical Practice Guidelines in Oncology also call for mRNA profiling as a diagnostic test. Quantifying RNA has become increasingly important in breast cancer, alongside IHC for Ki-67, a nuclear protein associated with cell proliferation. Increased levels of Ki-67 proteins are indicative of cell proliferation. It has also been shown that examining the RNA transcript levels give another sense of the proliferative rate of the tumor. Again, here is an opportunity to discern the likelihood of an aggressive cancer from a slower growing type and treat the patient accordingly.

All these tests are designed so that we can correctly stratify the risk to the patient and avoid overtreatment. It also means that tests need to be prioritized for efficiency and to maximize the information we collect from the small amount of sample. When we divide up the sample, some tissue goes off for H&E staining, some from RNA analysis, some for IHC imaging. The region of interest may be clearly visible on the sample surface, but a branching and convoluted structure that changes as it gets deeper into the tissue. There's always a chance we will miss something important because of how we dissected the sample and disrupted the tumor. With DSP Technology from NanoString, we don't have to make those compromises—we can potentially get all that information from one intact sample.

For more information, please visit nanostring.com/DSP

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