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Commentary: Tasting individual ingredients of meso soup: Can 'omics bring out the flavor?

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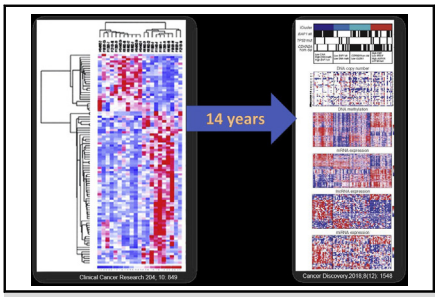

The meso-molecular landscape evolved from limited microarrays to multiomics in 14 years.

CENTRAL MESSAGE

An evolution of molecular biology techniques is broadening our understanding of mesothelioma. Molecular phenotyping will guide diagnosis, prognosis, as well as prediction of therapeutic response.

It's funny how things you say in the past come around to haunt you. In 2002, I wrote a commentary about the state of the art of surgery for mesothelioma, lamenting about the slow pace of clinical/surgical breakthroughs for the disease.[1] I did know, however, that the revolution in studying the genomics of the disease had already started in the Northeast, led by Bueno and Sugarbaker,[2] and it was only a matter of time (and money) before large, relevant, well-annotated series of patients with pleural mesothelioma would be "clustered" according molecular, rather than histologic, phenotype.[3-5]

It's 18 years later, and maybe the clues to what makes the difference in how patients do with pleural mesothelioma point to understanding basic pathways. This has sort of been the low-hanging fruit with this disease: these patients don't do very well with few exceptions; there isn't great therapy; surgery, although not defined by standard operating procedures from one place to the other, can help us figure out what's going on because we can use the evolution of next-generation sequencing and transcriptomics to define prognostic clusters. Essentially, despite the genomic revolution, the simplest of principles seems to hold: sarcomatoid does lousy and epithelial does better[6]; easy, so if you mix sarcomatoid and epithelial, you get biphasic, and its prognosis is variable. It's not that easy: if you mix red and green, you get yellow; if you mix epithelial and sarcomatoid, you don't get yellow, but you get a rainbow of possible outcomes.

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The molecular revolution, as so aptly defined by Severson and colleagues,[7] tries not to "get caught up in the details" (individual genes); it tries to take bundles of genes and see how they work or don't work together to create pathways, and these pathways become the rainbow of possibilities, blending and interacting with each other to determine an intermediate endpoint in an individual patient. Generalities can be made, however, for groups or "clusters" of patients that seem to be governed by the same pathways. These generalities are the fruits of the terabytes of data that have been published as illustrated by the timeline in the "Age of Omics," but the beauty of this exercise becomes relevant when you start to concentrate on those issues that could explain the variety of outcomes for these patients.

Severson and colleagues[7] give a powerful discussion of at least one of these "rainbow of possibilities" that could be the mother of all pathways for prognosis, which is known as epithelial mesenchymal transition (EMT). The beauty of this discussion is that 2 completely independent laboratories, working with completely different genomic algorithms, have seemed to come to the same conclusion. The rainbow of differences between epithelial and sarcomatoid outcomes, seen in the biphasic histology, is defined by genes, which can change cells from Jekyll to Hyde, ie, become much more invasive with the ability to

cross boundaries, and metastasize. High EMT with these types of genes is more like sarcomatoid; low EMT is more like epithelial; the revelation, however, is the gradient of EMT, as alluded to by the variation in the ratio of gene levels associated with EMT from the work of Bueno and colleagues (claudin and vimentin). The "ah-ha!" moment comes when Blum and colleagues[5] also devise an epithelial or sarcomatoid score from 150 genes derived from a methodology that essentially "orders" or deconvolutes the molecular tumor heterogeneity of the samples, and sure enough the epithelial score is associated with the claudins as detailed by the group of Bueno and colleagues.

So it's that easy, huh? No, it's not. Sure, we can subdivide patients into categories of high risk for failure or low risk for failure using a variety of the tools given to use by the molecular revolution, including claudin/vimentin ratios and epithelial/sarcomatoid deconvolution schemes, and they may even correlate with each other. However, the issues that remain include the margin of error in these predictions because they may not have the sensitivity and specificity for individual personalized prognostication. Moreover, mesothelioma is polyclonal,[8,9] and if we were to base our predictions solely on a single biopsy, how do we know what the molecular phenotype is in other areas of the tumor? Of course I am nit-picking, and you don't have to convince me how important the evolution of 'omics will be not only in prognosticating patients, but in finding better markers for therapy, including those for immunotherapy of mesothelioma with or without chemotherapy.[10] There is where the rubber meets the road …accurate prediction of therapy using the mesothelioma 'omics revolution. Better yet is the accelerating pace of discovery at a number of international 'omics laboratories for improved strategies for mesothelioma.[11-13]

Oh well…a continuing and evolving explosion of molecular insight in pleural mesothelioma.

Who knew?

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