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Computer assisted spectral karyotyping and its promising clinical application

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In this issue of Convergent Science Physical Oncology, Dayal et al [1] have utilized high throughput computer assisted spectral karyotyping to analyze tumor heterogeneity in cutaneous squamous cell carcinoma (SCCT), the second most common skin cancer after basal cell carcinoma. Though this type of skin cancer is not generally fatal, in its advanced stage its removal can be disfiguring. For this article, the investigators are using this cell line as a model to develop faster (high throughput) methods to understand the genetic diversity that exists pre- versus post-treatment in these cell lines. However, the methods developed here could be applied to other types of cancer as well. Though spectral karyotyping has gained in popularity over the last 8 years (over 922 papers have been published in this area since 2007), unless the technique can be reproducibly applied and automated, it will not be part of the routine analysis needed in tumor pathology.

The development of computational methods to allow for computer-assisted spectral karyotyping will enable investigators to quickly and accurately track genetic changes in tumor cell populations. In this work, keratinocytes are studied before and after exposure to ultraviolet (UV) light or the commonly used chemotherapeutic, doxorubicin (a.k.a. ‘The Red Devil’). UV exposure should drive genetic changes to the original cancer cells, which will increase their overall heterogeneity (the number of different types of cells present). Similarly, the diversity of the cell population is also expected to increase after treatment of the parent cell population with doxorubicin. The authors compare the population of two different tumor cell types (SCCT1 and SCCT8) and normal blood. Prior studies had already shown that the degree of heterogeneity of the two cell types was different (SCCT8 ≫ SCCT1), so this allows the investigators to test their methods using known population distributions. Principal component analysis (PCA), a commonly used mathematical data analysis method, was used to analyze the cell populations and quantitatively characterize the degree of heterogeneity in different cell populations. The authors then move forward by inducing heterogeneity through the use of UV light or doxorubicin. The induced genetic changes in SCCT1 cells present after ‘treatment’ now more closely mimics that seen in the original untreated SCCT8 cells. The authors suggest that these observed changes could be driven by one of two methods; either (A) new clones emerge from damage to the original cancer cell’s DNA, or (B) there is an increase in the population of previously undetected (minority) clones that occurs after cells that are sensitive to doxorubicin are destroyed. In either case, this technique will allow clinicians to determine whether a patient’s tumor cells are generally of a homogeneous type or more of a heterogeneous population.

As a metastatic cancer patient, I can envision that this type of data may find great applicability in the clinic in the not-so-distant future. I will use the case of metastatic breast cancer, since this is the area with which I am most intimately familiar. Approximately 10% of metastatic patients already have metastases upon initial diagnosis (de novo metastatic disease). When these patients present with a tumor within her or his breast, they also have tumors within other sites. The most common sites for metastases are the bones, lungs, the liver, and the brain (most common with HER2 + and triple negative disease) [2]. Often each site of metastasis must be biopsied to ensure that the genetic markers present in one site are the same as those in another. Having the ability to dig even deeper and quickly determine the degree of karyotype heterogeneity between cancer cells present in the breast versus those present in other sites may allow for more personalized and improved treatment for those with metastatic disease. Given that there is currently no cure for metastatic disease, these patients remain in treatment for the rest of their life and therefore remain a significant challenge to oncologists that are looking to improve the long term effectiveness of a patient’s treatment. For example, if a patient presents with highly heterogeneous tumors, it may motivate the oncologist to try a multi-pronged approach in treating the patient’s cancer to prevent the initial treatment from creating a favorable growth environment for diverse clones by actually wipe out...
the cells that are most sensitive to that flavor of treatment. This event happens frequently when a metastatic patient shows a great response in their lung metastases (for example), but their liver metastases continue to grow. Even for early stage patients, if we knew from the start that a particular patient had a very heterogeneous tumor, we would know that their disease may be likely to lead to metastasis in the future. This could help us prevent the 25–30% of those patients that begin as early stage that eventually move on to advanced disease. This type of data could also be used to investigate how a patient’s tumor is responding to initial treatment and whether genetic diversity is increasing as a function of treatment time.

Though this study provides initial excitement for the development of methods to aid in treating highly heterogeneous cancers, there remain long-term challenges that can be foreseen in the clinical application of this technology. One of those challenges that can be envisioned is that the technology that has been developed by Dayal et al and presented in this issue has been explored using a very homogeneous primary cell population and has not really been tested in a solid human tumor. Solid tumors will be extremely heterogeneous by nature [3], since they are composed of a mixture of stroma, blood cells, immune cells, and fat cells among other types of cells. Therefore, it is unclear whether the computer assisted spectral karyotyping method described by Dayal et al will be sufficiently sophisticated to differentiate between these very diverse cell types. It would be of interest to understand how these methods will be adapted to a real tumor sample. However, given that spectral karyotyping is starting to be applied in the study of metastatic disease in other models [4], there is hope that the advancements present in this new work can be successfully applied to metastatic disease.

References