News

Treatment

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course.

This is called "precision medicine," and it has had some successes in breast cancer treatment. Many biomarker-based, or precision, therapies are now standard of care. But this field needs to be expanded further to improve overall patient outcomes.

Not only are tumors are different from one another, but there can even be genetic differences within a single tumor. These differences between tumors and within them are called tumor heterogeneity.

Our lab at Michigan State University, under the direction of Eran Andrechek, is studying how best to define the tumor heterogeneity and the effect that these differences have on a patient's

Jonathan Rennhack, pictured here, is part of a team of researchers focusing on identifying biomarkers in breast cancer tumors.

response to therapy. In particular, we are using next-generation technologies to understand tumor heterogeneity and define better treatment strategies for patients.

Tumor diversity makes treatment complexTo devise a better treatment strategy we have to understand how heterogeneity within and between tumors arise in the first place.

Tumors are a result of uncontrolled division of a single cell. However, a tumor is not the same throughout. Even though it starts with a single cell, the cells that make up the tumor are not all identical.

As a tumor cell divides, each daughter cell has mutations not present in the parent cell. This is called genetic instability. This multitude of mutations leads to a survival-of-the-fittest scenario within the tumor (this is called selective pressure).

Some of these mutations give cells an edge over other cells. Selective pressure means that cells with certain characteristics "win" the survival of fittest battle within the tumor. The result is that different "neighborhoods" of the tumor will be populated with clones of the fittest cells. Perhaps one region of the tumor is low in nutrients; it will contain cells that have picked up mutations to survive in a low nutrient environment. Another region might be under constant exposure to the body's immune system; it will contain cells with immune evasion mutations. This is how differences within tumors emerge, and this diversity is also one reason why each patient's tumor is unique, and subsequently why their tumor's vulnerability to therapy is different, too.

This genomic instability also exists between patients. A combination of random chance and differences in the genome lead to unique tumors to develop in each patient. Let's say, for example, that we are looking at a group of breast cancer patients whose tumors all have the same biomarker.

Some patients have a complete response to a particular treatment tailored to that biomarker, meaning that the tumor shrinks and the patient is in remission.

> "[Precision medicine] needs to be expanded further to improve overall patient outcomes.

But one treatment does not fit all patients with the same biomarker. For instance, other patients with that same biomarker may respond to the same treatment at first, but then their tumor grows back because it has become resistant to the original therapy. This is due to what is called intra-tumor heterogeneity, which refers to genetic differences within the tumor, thanks to the genetic instability and survival of the fittest that we described earlier. One region of a tumor may have one genetic change, while other regions of the tumor have a different change. This leads to one region of a tumor responding to a treatment while another region of the tumor will not.

Other patients may have little or no response to the treatment that led to remission in patients with the same biomarker, or at least worked initially in other patients. For instance, we have found that the same genes give the tumor different characteristics in two different subtypes of breast cancer (basal and HER2 positive). The difference between tumors from one patient to another, inter-tumor heterogeneity, is a complicating factor in our current cancer treatment therapy based upon biomarkers.

Therefore, the genetic heterogeneity both between tumors and within tumors is a critical factor to be considered in developing suitable treatments.

Sequencing tumors to find better treatmentsIn the Andrechek lab we have used whole genome sequencing and microarray technology chip for examining gene expression data, to understand what the genomic profile of different regions of the tumor look like.

We can look at mutations, changes in the number of copies of certain genes or translocation, which is when genes aren't in the place they should be.

Perhaps more importantly, we have worked to understand the impact of those mutations on all of the genes produced by a tumor cell, called the transcriptome.

This is important because the transcriptome contains the majority of the instructions the tumor needs to grow and survive.

We noted that disruption of the expression of one particular gene promotes the formation of tumors as well as slows the tumor growth in a model of breast cancer. The combination of genes that a tumor takes advantage of to grow are referred to as key oncogenic pathways.

If we can profile these pathways and identify which ones are active in a tumor, that could let us design individualized therapies to target them.

Our results showed that through the use of targeted genomic therapy, we inhibited tumor growth in each group. Then we expanded our study to analyze more than 1,000 tumors from breast cancer patients, and we noticed significant shrinkage of tumors. In these trials, we are also able to understand intra-tumor heterogeneity through profiling the genetic changes after treatments. This showed the selective pressures a treatment creates on the different types of cells in a tumor.