Researchers: Darwin's principles say cancer will always evolve to resist treatment

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According to researchers at Moffitt Cancer Center, cancer is subject to the evolutionary processes laid out by Charles Darwin in his concept of natural selection. Natural selection was the process identified by Darwin by which nature selects certain physical attributes, or phenotypes, to pass on to offspring to better "fit" the organism to the environment.

As applied to cancer, natural selection, a key principle of modern biology, suggests that malignancies in distinct "microhabitats" promote the evolution of resistance to therapies. However, these same evolutionary principles of natural selection can be applied to successfully manage cancer, say Moffitt researchers who published an opinion piece in a recent issue of *Nature Reviews Cancer*.

"Understanding cancer as a disease starts with identifying crucial environmental forces and corresponding adaptive cellular strategies," said Robert A. Gatenby, M.D., chair of the Department of Diagnostic Imaging. "Cancer is driven by environmental selection forces that interact with individual cellular adaptive strategies."

Cancer cell development, like any natural selection (or Darwinian) process, is governed by environmental selection forces and cellular adaptive strategies, the authors wrote. Investigating cancer and its proliferation through genetic changes and ignoring the adaptive landscape is most likely futile. Under "selective pressure" of chemotherapy, in this case the "adaptive landscape," resistant populations of cancer cells invariably evolve.

The authors say that tumors can be thought of as "continents" populated by multiple cellular species that adapt to regional variations in environmental selection forces. Their strategy in offering this metaphor, they wrote, is to "integrate microenvironmental factors at work during cancer's progression" into the model of the evolution of cancer and, particularly, the evolution of drug resistance.

"Hundreds of mutations can be found in tumors," said co-author Daniel Verduzco, Ph.D., a post-doctoral fellow at Moffitt. "The physical environment of the early tumor is constantly changing, often in response to inflammation."

This reality should remind us, they wrote, that natural selection selects for phenotype, for observable physical characteristics, and that natural selection forces at work in local environments causes populations to change phenotypically rather than genotypically.

The authors point out that for most patients with advanced cancers - even when there is a well-known target and a highly specific drug - response to therapy is fleeting owing to the evolution and proliferation of a resistant population of cancer cells.

While targeted therapies have been among the most recent approaches to treating cancer, the authors suggest that the vast changes in the genetics of tumors via mutations reduce the effectiveness of targeted therapies and are a reason why targeted therapies cease to work.

"The emergence of resistance is predictable and inevitable as a fundamental property of carcinogenesis," Gatenby said. "However, this fundamental fact is commonly ignored in the design of treatment strategies. The emergence of drug resistance is rarely, if ever, dealt with until it occurs."

In an effort to develop patient-specific, long-term therapeutic strategies, the authors contend that resistance should be anticipated. By "anticipation" in action, they mean developing "adaptive therapies" prior to the emergence of resistance.

Cancer cells, they wrote, can only adapt to immediate selection forces. Cancer cells cannot anticipate future environmental conditions or evolutionary dynamics. This concept, said the authors, may provide an advantage when designing new therapies by "directing" the natural selection processes to prevent the outgrowth of resistant cancer populations and so improve outcomes.

"This potentially unifying theory places the evolution of cancer within a dynamically active landscape," said Robert J. Gillies, chair of the Department of Cancer Imaging and Metabolism, and program leader of Experimental Therapeutics. "The outcome is cancer's heterogeneity - those variations that negatively affect targeted therapies to control cancer.

"Recognizing that evolutionary dynamics are an essential component of carcinogenesis itself can lead to development of appropriate therapeutic strategies," Gillies said. "For example, knowing ahead of time that resistant cancers are likely to emerge provides us with lead time to develop preventive or adaptive therapeutic approaches. We have recently completed studies with our colleagues, Dr. Ariosto Silva , showing that evolutionarily informed therapies can forestall the emergence of resistant tumors for a very long time."

The authors conclude that we can use our understanding of evolution to strategically direct natural selection toward preventing the outgrowth of resistant cancer populations and, in so doing, improve outcomes.

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