Stressed out: Scientist details cells' response to lesions

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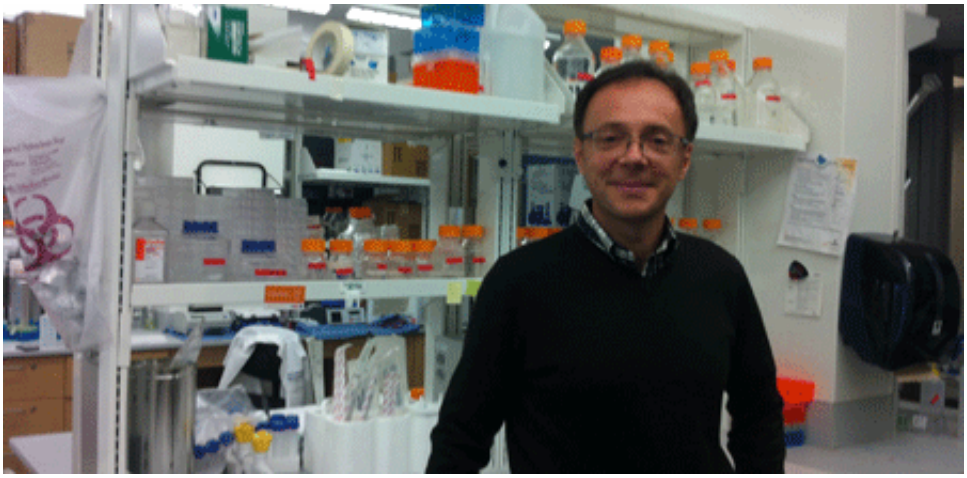

Alessandro Vindigni, Ph.D., professor of biochemistry and molecular biology at Saint Louis University. Credit: Saint Louis University

In a recent review paper published in *Nature Structural & Molecular Biology*, SLU scientist Alessandro Vindigni, Ph.D., describes the strategies cells use when their DNA faces replication stress, challenges that may derail a cell's ability to reproduce. In this do-or-die situation, cells have several tactics that can help them overcome lesions or other obstacles in order to ensure faithful transmission of their genetic information.

Vindigni, who is professor of biochemistry and molecular biology at Saint Louis University, says that several molecular pathways help

maintain genome stability, preventing or limiting cancer and premature aging.

"Deciphering the mechanisms that cells use to faithfully replicate our genome and cope with DNA lesions is integral to the diagnosis and treatment of several human diseases," said Vindigni.

For a cell, stress comes in the form of DNA lesions, which can occur as often as 100,000 times per cell per day. They can be the result of normal metabolic activities, like free radicals, as well as exposure to environmental factors such as UV radiation, X-rays and chemical compounds.

DNA replicates by unzipping its two interwoven strands and making copies of each. As the DNA strands separate and copy, they form a "replication fork." Sometimes, these forks run into obstacles - like lesions - that block their progress.

While lesions pose serious threats, our cells have evolved elegant mechanisms to cope, Vindigni says.

In the paper, Vindigni details several coping strategies cells use when they face replication stress: the cellular version of choosing yoga, meditation or a trip to the movies after a stressful event.

The cellular stress-busters include fork repriming, fork reversal, fork degradation and backtracking, replication-fork breakage, and replisome dynamics during replication-fork restart. These approaches all give cells a chance to fix the obstacles in their paths and avoid passing along a genetic mistakes to their daughter cells.

Improper repair of DNA lesions can lead to mutations, abnormal chromosome structures, or loss of genetic information that in turn can

cause premature aging, cancer and genetic abnormalities.

Depending on the degree of genome instability, these alterations will determine whether a cell survives, goes into a growth-arrest state, or dies.

Scientists are still discovering additional causes of replication stress and the pathways a cell's replication machinery can use to respond to them. Vindigni's paper details several recently discovered pathways; now, researchers want to learn more about how a cell chooses a strategy.

Understanding more about how cells react to replication stress will be key to designing future therapies, particularly for cancer, Vindigni predicts.

More information: Matteo Berti et al. Replication stress: getting back on track, *Nature Structural & Molecular Biology* (2016). DOI: 10.1038/nsmb.3163

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