Inhibition of DNA Repair Slows Cancer Progression

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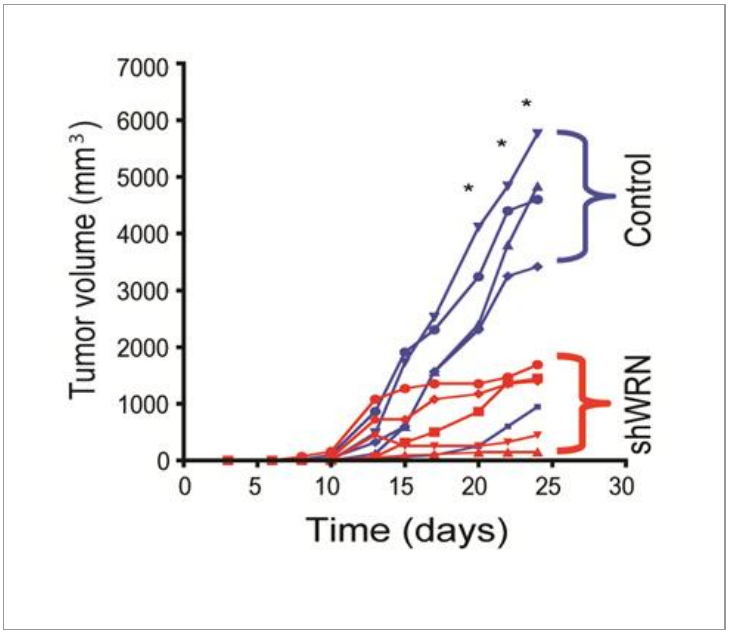
Myc is a transcription factor whose ability to activate cell growth and DNA replication is tightly regulated in healthy cells. When Myc is deregulated (e.g., through overexpression), its activity can lead to genomic instability, uncontrolled growth and ultimately cancer. There are multiple cellular mechanisms in place to trigger apoptosis in response to aberrant Myc activity (e.g., Myc-induced DNA damage may activate apoptotic pathways via the tumor suppressor p53). Unfortunately, many aggressive human cancers frequently harbor concurrent genetic changes that disable these pathways (e.g., inactivating mutations in p53). It is thus of great interest that research technician Russell Moser, principal investigator Dr. Carla Grandori and colleagues in the Human Biology Division have identified a mechanism for reducing cancer development in the context of both Myc overexpression and p53 inactivation.

Grandori and colleagues previously found that Myc activates the transcription of WRN, a DNA helicase/exonuclease that repairs DNA replication errors. In the absence of WRN, Myc overexpressing cells are driven to senescence through DNA damage sensing pathways. These findings led Moser *et al.* to investigate whether silencing of WRN could inhibit the development of Myc-driven tumors *in vivo*. Using two different mouse models of cancer, they showed that silencing of WRN leads to a) reduced tumor growth in xenografts of a human lung cancer cell line that expresses high levels of Myc and b) increased median survival of mice that rapidly develop lymphomas due to constitutive Myc expression in lymphoid precursor cells (115 days compared to 151 days if WRN is inactivated at the germ-line). Moreover, the authors found significantly higher levels of a DNA damage marker, reduced levels of proliferation and no signs of increased apoptosis in the WRN silenced models compared to controls. This trend held true even after stratifying for p53 mutations in late onset lymphomas from the second mouse model. Taken together, these results suggest that WRN may be a valuable therapeutic target for cancers driven by Myc-deregulation, including those that exhibit p53 mutations.

What, then, is the consequence of WRN inhibition in humans? Nature has already performed this experiment, as individuals suffering from Werner Syndrome possess inactivating mutations in *WRN*. These individuals exhibit accelerated aging, cellular senescence, and genetic instability, and also

suffer from rare types of cancer. In contrast, *WRN* deficient mice are not predisposed to spontaneous tumor development. These two seemingly contradictory observations may be explained by the delayed onset of Werner Syndrome, which is approximately 15 years in humans. Short term WRN inhibition for cancer therapy might thus preclude Werner Syndrome like effects, and anyway, such effects may be worth the risk to individuals suffering from aggressive Myc-driven cancers. For example, neuroblastoma cases are already screened for Myc overexpression, as this phenotype is associated with more aggressive cancer.

Moser R, Toyoshima M, Robinson K, Gurley KE, Howie HL, Davison J, Morgan M, Kemp CJ, Grandori C. 2012. Myc-driven tumorigenesis is inhibited by WRN syndrome gene deficiency. *Molecular Cancer Research*, Epub ahead of print, doi: :10.1158/1541-7786.MCR-11-0508



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In mice that developed tumors from xenografts of a human lung cancer cell line expressing high levels of Myc, treatment with an shRNA against the WRN DNA repair helicase to downregulate WRN expression (shWRN) significantly stunted tumor growth compared to treatment with a negative control shRNA (Control). * $p < 0.05$