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# Effect of mutant p53 stability on tumorigenesis and drug design

May 15 2008

In the May 15th issue of G&D, Dr. Guillermina Lozano (MD Anderson Cancer Center) and colleagues reveal how the stabilization of a mutated form of p53 affects oncogenesis, and lends startling new insight into the potential pitfalls of using Mdm2 inhibitors for cancer therapy.

"Our data are both exciting and sobering: we must classify tumors with respect to p53 mutation status prior to treatment," emphasizes Dr. Lozano.

One function of the p53 tumor suppressor is to arrest the cell cycle in response to DNA damage. For years it has been the focus of intense cancer research, as mutations in p53 prevent cell cycle arrest and lead to unregulated cell growth. p53 is one of the most commonly mutated genes in human cancers.

Dr. Lozano's research team now demonstrates how a particular mutated form of p53 – which is prevalent in human cancers – can become stable in some cells, where it facilitates cancer formation and metastasis. The scientists found that mutant p53 is inherently unstable in normal tissues, but can become stable in some cells.

The researchers discovered that the acquisition of additional mutations the p53-antaogonist, Mdm2, could effectively stabilize mutant p53. Transgenic mice engineered to harbor such mutations displayed enhanced tumor formation and metastasis, compared with littermates lacking only p53.

Targeted drug therapies aimed at activating p53 tumor suppressor activity via the disruption of the normal Mdm2/wild-type-p53 interaction will also disrupt the Mdm2/mutant-p53 interaction. Thus, these Mdm2 inhibitors will succeed in stabilizing mutant p53, and fail in preventing tumor metastasis.

Source: Cold Spring Harbor Laboratory