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ISG15 ACCELERATES REPLICATION FORK PROGRESSION

The ubiquitin-like molecule ISG15, which is induced by interferons and is often upregulated in cancer cells, can increase genome instability and sensitize cells to genotoxic drugs

ISG15 is strongly induced by type I and type III interferons in response to bacterial or viral infection. Though its amino acid sequence is very different, ISG15's 3D structure is similar to ubiquitin and, like ubiquitin, it can be conjugated to other proteins by E3 ligases. But increasing evidence suggests that ISG15 can modulate the host immune response by non-covalently binding to other proteins or even by acting as a cytokine secreted from cells.

ISG15 is also induced by DNA damage and is frequently overexpressed in cancer cells. "Elevated *ISG15* levels occur in many types of cancer and, in some cases, the robust expression of *ISG15* has been reported to support tumor growth," explains Lorenza Penengo from the Institute of Molecular Cancer Research at the University of Zurich. "However, its role in tumorigenesis is still controversial, and its mechanism of action is far from being clarified."

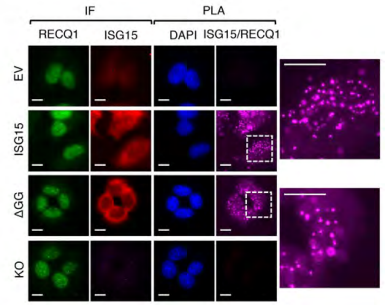
Penengo and colleagues, including first author Chiara Raso, discovered that ISG15 localizes to DNA replication forks, suggesting that it might modulate DNA replication. Inducing *ISG15* expression accelerated fork progression, whereas deleting the gene reduced the speed of DNA replication in several cancer cell lines that usually overexpress *ISG15*.

Raso et al. determined that ISG15 can regulate DNA replication fork progression through non-covalent mechanisms: overexpression of a mutant version incapable of being conjugated to other proteins still accelerated fork progression.

The researchers found that ISG15 associates with several proteins at replication forks, including a DNA helicase, RECQ1, that helps to restart stalled forks. "Depletion of RECQ1 completely abolished the accelerated replication fork progression induced by high levels of ISG15, suggesting that ISG15 may regulate RECQ1 function by unleashing its restart activity," Penengo says. Indeed, increased ISG15 levels promoted fork restart in a RECQ1-dependent manner.

Elevated *ISG15* might therefore be detrimental to cancer cells by causing DNA replication to continue in the presence of genotoxic drugs that would normally slow replication fork progression, resulting in genomic instability. Raso et al. found that cancer cells with high ISG15 levels were more sensitive to low doses of the chemotherapeutic agents camptothecin and cisplatin, because their replication forks continued unabated, leading to chromosome breakages and cell death.

"The increased activity of RECQ1 induced by high ISG15 levels may thus represent an important vulnerability that can be exploited for genotoxic anticancer treatments," Penengo says. "Furthermore, the evaluation of ISG15 levels in tumor samples may represent a predictive parameter to stratify patients in personalized cancer therapy."



Proximity ligation assays (magenta) show that ISG15 (red) associates with the DNA helicase RECQ1 (green) in cells, even when the cells express a mutant version of ISG15 (ΔGG) that cannot be covalently conjugated to other proteins.

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ORIGINAL PAPER

Raso, M.C., N. Djoric, F. Walser, S. Hess, F.M. Schmid, S. Burger, K.-P. Knobeloch, and L. Penengo. 2020. Interferon-stimulated gene 15 accelerates replication fork progression inducing chromosomal breakage. *J. Cell Biol.* 219: e202002175.

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