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GENOME INSTABILITY

Stress management by the FA pathway

The stalling of replication forks can cause DNA damage and genome instability. The tumour suppressive Fanconi anaemia (FA) pathway is known to have a role in stabilizing replication forks, but the nature of the endogenous lesion that recruits members of the FA pathway in normally replicating cells has remained elusive.

Schwab *et al.* hypothesized that the FA pathway might provide replication fork protection upon encountering actively transcribed genes. They showed that cells lacking FANCD2 (a central component of the FA pathway known to be activated when replication is stalled) or an upstream core pathway member, FANCC or FANCA, had increased replication fork instability and DNA breaks under normal growth conditions; these defects could be reversed upon inhibition of transcription. In addition, FANCD2 colocalized with RNA polymerase II, and several methods of inhibiting transcription decreased activation of the FA pathway in wild-type cells.

> “the FA pathway suppresses DNA–RNA hybrids”

During transcription, DNA–RNA hybrids form that can stall replication and promote genome instability. The authors noted that levels of DNA–RNA hybrids increased in cells lacking a functional FA pathway, and removal of these hybrids by overexpression of RNase H1 prevented activation of the FA pathway in cells undergoing normal replication. RNase H1 also prevented the replication fork instability and DNA breaks that the authors had observed in cells that lacked FANCD2. DNA damaging agents can induce DNA–RNA hybrids, so the authors examined aldehydes, which have been shown to induce DNA damage and contribute to leukaemia formation in mice lacking the FA pathway. Treatment of FANCD2-deficient cells with low doses of formaldehyde that were non-toxic to normal cells increased levels of DNA–RNA hybrids, which could explain the genotoxic effects of aldehydes. Together, these data suggest that the FA pathway suppresses DNA–RNA hybrids, leading to reduced DNA damage.

Further analyses showed that the FA pathway has a dual role in ensuring faithful replication through sites of active transcription, as the FA pathway not only stabilizes stalled replication forks but can also directly resolve DNA–RNA hybrids. The authors looked at the role of FANCM, which is a double-stranded DNA translocase, hypothesizing that FANCM might also have activity on DNA–RNA hybrids. Indeed, cells lacking FANCM had increased DNA–RNA hybrids, and purified FANCM could unwind DNA–RNA hybrids in a manner dependent on its translocase activity.

This study suggests that the FA pathway might prevent genome instability by stabilizing replication forks when actively transcribed DNA is encountered and by removing DNA–RNA hybrids. The disruption of these processes in patients with FA might contribute to their cancer predisposition.

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ORIGINAL RESEARCH PAPER Schwab, R. A. *et al.* The Fanconi anemia pathway maintains genome stability by coordinating replication and transcription. *Mol. Cell* http://dx.doi.org/10.1016/j.molcel.2015.09.012 (2015)