Telomere dysfunction puts the brakes on oncogene-induced cancers

Cagatay Günes¹ and Karl Lenhard Rudolph^{1,2,*}

¹Institute of Molecular Medicine and Max-Planck-Research Group on Stem Cell Aging, Ulm, Germany and ²Leibniz Institute of Age Research—Fritz-Lipmann Institute (FLI), Jena, Germany

*Correspondence to: KLRudolph@fli-leibniz.de

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Senescence represents a major tumour suppressor checkpoint activated by telomere dysfunction or cellular stress factors such as oncogene activation. In this issue of *The EMBO Journal*, Suram *et al* (2012) reveal a surprising interconnection between oncogene activation and telomere dysfunction induced senescence. The study supports an alternative model of tumour suppression, indicating that oncogene-induced accumulation of telomeric DNA damage contributes to the induction of senescence in telomerase-negative tumours.

Telomere shortening limits the proliferative capacity of primary human cells after 50–70 cell divisions by induction of replicative senescence activated by critically short, dysfunctional telomeres. Different mechanisms were thought to initiate senescence in response to oncogene activation, which occurs abruptly within a few cell doublings (Serrano *et al*, 1997). Oncogene-induced senescence (OIS) involves an activation of DNA damage signals at stalled replication forks induced by DNA replication stress (Bartkova *et al*, 2006; Di Micco *et al*, 2006). Replication fork stalling in response to oncogene activation preferentially affects common fragile sites of the DNA (Tsantoulis *et al*, 2008). The ends of eukaryotic chromosomes—the telomeres—represent common fragile sites that are sensitive to replication fork stalling (Sfeir *et al*, 2009). These data made it tempting to speculate whether replication fork stalling at telomeres was causatively involved in OIS. Studies on replicative senescence in human fibroblast also supported this possibility showing that mitogenic signals amplify DNA damage responses in senescent cells (Satyanarayana *et al*, 2004).

Multiple studies revealed experimental evidences that senescence suppresses tumour progression in mouse models and early human tumours (for review see Collado and Serrano, 2010). The relative contribution of OIS and telomere dysfunction induced senescence (TDIS) to tumour suppression and possible interconnections between the two pathways at the level of checkpoint induction were not investigated in previous studies. In this issue of *The EMBO Journal*, Suram *et al* (2012) describe the presence of TDIS in human precursor lesions but not in the corresponding malignant tumours. Mechanistically, the study shows that oncogenic signals cause replication fork stalling, resulting in telomeric DNA damage accumulation and activation of DNA

damage checkpoints reminiscent to TDIS. Telomerase expression does not rescue replication fork stalling but prevents the accumulation of DNA damage at telomeres allowing a bypass of OIS.

The study has several important implications for molecular pathways and therapeutic approaches in cancer that need to be further explored (Figure 1):

(i) Telomere length independent roles of telomeres in tumour suppression

The classical model of telomere-dependent tumour suppression indicates that proliferation-dependent telomere shortening leads to telomere dysfunction, activation of DNA damage checkpoints, and induction of senescence suppres-

Figure 1 Traditional and new models of senescence in tumour suppression. **(A)** Traditional model of replicative senescence: Telomerase-negative tumour cell clones experience telomere shortening as a consequence of cell division. After a lag period depending on the initial telomere length, tumour cells accumulate telomere dysfunction and activation of senescence impairs tumour growth. Telomerase activation represents a late event allowing tumour progression. **(B)** New model of oncogene induced, telomere-dependent senescence: Oncogene activation leads to abrupt accumulation of DNA damage at telomeres resulting in senescence and tumour suppression. Telomerase-positive stem cells could be resistant to OIS and may be selected as the cell type of origin of tumour development.

sing the growth of telomerase-negative tumour clones. Studies on mouse models supported this concept showing that telomere shortening impairs the progression of initiated tumours in a telomere length-dependent manner (Feldser and Greider, 2007). The new data from Suram *et al* (2012) indicate that oncogene-induced replication fork stalling activates a telomere-dependent senescence checkpoint, which is independent of telomere length. The study shows that replication forks stall in response to oncogene activation throughout the genome. However, stalled replication forks are resolved in non-telomeric regions, whereas fork stalling inside telomeres leads to un-repairable DNA damage in telomerase-negative cells. These findings are in line with recent publication showing accumulation of un-repairable DNA damage in telomeric DNA in response to aging and stress-induced DNA damage (Fumagalli *et al*, 2012).

(ii) Telomere length independent roles of telomerase in tumour progression

Following the classical model telomeres in tumour suppression (Figure 1A), telomerase re-activation is required for tumour progression by limiting telomere dysfunction and the induction of DNA damage checkpoints in response to telomere shortening. The new data from Suram *et al* (2012) indicate that telomerase has an additional telomere length independent role in tumour progression. The study shows that catalytically active telomerase prevents the activation of DNA damage signals originating from stalled replication forks

inside telomeres in response to oncogene activation (Figure 1B). The exact mechanisms of telomerase-dependent healing of stalled replication forks at telomeres remain to be elucidated. It is also unclear whether telomerase activity can prevent any type of DNA damage at telomeres as an over-expression of TERT could not suppress irradiation-induced cellular senescence or the persistence of telomeric DDR following irradiation, H₂O₂, or chemotherapy induced DNA damage (Hewitt *et al*, 2012).

The data could provide a plausible explanation for the increased tumorigenesis in telomerase transgenic mice—a finding which is difficult to explain by telomere length dependent effects of telomerase given the long telomere reserves in mouse tissues (Gonzalez-Suarez *et al*, 2001). According to the findings of Suram *et al* (2012), anti-telomerase therapies could have immediate anti-cancer effects in tumours depending on telomerase-mediated healing of stalled replication forks at telomeres. Specific markers for this dependency could be of clinical value. In addition, the data support the concept that somatic stem cells could represent the cell type of origin of cancers. In contrast to differentiated somatic cells, tissues stem cells are often telomerase-positive, indicating that stem cells might be less sensitive to OIS.

Conflict of interest

The authors declare that they have no conflict of interest.

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