The Cell Cycle in Cancer: Molecular Pathways, Checkpoint Aberrations, and Therapeutic Opportunities

Detina ZALLI
Academic Director for the Pre-Medical Studies course at the University of Cambridge, UK
Corresponding author: Detina Zalli
E-mail: detinazalli@gmail.com

Jonila GABRANI
Centre for Scientific Research,
Faculty of Medical Technical Sciences,
European University of Tirana

Abstract

The eukaryotic cell cycle is a finely orchestrated sequence of events ensuring accurate DNA replication and equal segregation of chromosomes. Dysregulation of this system lies at the heart of malignant transformation and cancer progression. Here, we provide an in-depth synthesis of the genetic, epigenetic, and biochemical alterations that affect cell cycle regulation in cancer, emphasising oncogene activation, tumour suppressor inactivation, and disruption of checkpoint fidelity. We explore the molecular mechanisms by which these perturbations foster replication stress, genomic instability, and aneuploidy. Furthermore, we review emerging therapeutic strategies that target these vulnerabilities, including inhibitors of cell cycle kinases, replication stress response mediators, and chromosomal segregation checkpoints. By integrating foundational discoveries with contemporary insights, this review elucidates the central role of cell cycle dynamics in oncogenesis and its therapeutic exploitation.

Introduction

Cell proliferation is fundamental to organismal development, tissue homeostasis, and regeneration. The eukaryotic cell cycle comprises a series of well-defined phases—G1 (gap 1), S (DNA synthesis), G2 (gap 2), and M (mitosis)—each governed by precise molecular machinery. Progression through these phases depends on the dynamic interaction between cyclins, cyclin-dependent kinases (CDKs), CDK inhibitors (CKIs), transcription factors, and DNA damage response (DDR) proteins. Temporal control of these interactions ensures proper DNA replication, accurate chromosome segregation, and maintenance of genomic integrity (Malumbres & Barbacid, 2009).

Each phase of the cell cycle is stringently regulated. In G1, cells evaluate extracellular signals and intrinsic stressors to decide whether to proceed to DNA replication. The transition from G1 to S phase is orchestrated by CDK4/6-cyclin D and CDK2-cyclin E complexes, which sequentially phosphorylate the retinoblastoma protein (pRB), leading to release of E2F transcription factors and activation of S-phase gene transcription (Sherr & McCormick, 2002). During S phase, origin licensing and helicase activation enable DNA synthesis, while the replication fork machinery must coordinate with histone deposition, transcription, and repair pathways to maintain fidelity. The G2 phase serves as a checkpoint to ensure complete replication and repair of any damage incurred. Finally, mitosis involves highly coordinated structural changes in chromosomes and the mitotic spindle to allow equitable segregation of sister chromatids (Morgan, 2007).

Cancer emerges when this regulation fails. Mutations in cell cycle regulators disrupt the balance between proliferation and quiescence, favoring uncontrolled division and survival of genetically unstable cells. These events are often driven by gain-of-function mutations in oncogenes, such as MYC and RAS, and loss-of-function alterations in tumour suppressors like TP53 and RB1 (Hanahan & Weinberg, 2011). Oncogene-induced signals often override physiological constraints, driving inappropriate proliferation and rendering cells refractory to anti-proliferative cues. Additionally, defects in key checkpoints—G1/S, intra-S, G2/M, and the spindle assembly checkpoint (SAC)—permit the propagation of replication errors and aneuploid progeny (Kastan & Bartek, 2004).

Cell cycle deregulation also fosters additional hallmarks of cancer, including resistance to apoptosis, increased metabolic demands, and immune evasion. As tumors evolve, subclonal populations develop differential reliance on specific cell cycle pathways, creating both complexity and opportunity for targeted intervention. Recent advances in single-cell genomics, functional screening, and synthetic lethality have deepened our understanding of cell cycle dependencies

in cancer and identified novel therapeutic targets (Nijman, 2011; Lawson et al., 2020). Thus, elucidating the disrupted cell cycle machinery in cancer not only provides insight into disease pathogenesis but also reveals critical vulnerabilities that may be exploited therapeutically.

Oncogenic Deregulation of Cell Cycle Control: The Roles of MYC and RAS

MYC: A Central Transcriptional Regulator in Proliferation and Tumorigenesis

The MYC oncogene encodes a basic helix-loop-helix leucine zipper (bHLH-LZ) transcription factor that regulates genes involved in nearly all aspects of cell physiology, including cell cycle progression, metabolism, protein synthesis, and apoptosis. MYC forms heterodimers with MAX and binds to canonical E-box sequences (CACGTG) in the promoter regions of target genes, leading to chromatin remodelling and transcriptional activation (Dang, 2012).

In cancer, MYC is frequently overexpressed due to gene amplification, chromosomal translocations, or dysregulated upstream signalling pathways (e.g., WNT, RAS, or PI3K/AKT). For example, translocations involving the immunoglobulin heavy chain locus and MYC (t(8;14)(q24;q32)) are characteristic of Burkitt lymphoma (Taub et al., 1982). Constitutive MYC expression results in the upregulation of genes encoding cyclins (e.g., CCND1, CCNE1), CDKs, and E2F transcription factors, which collectively accelerate G1/S transition. Additionally, MYC represses CDK inhibitors such as p21 and p27, further dismantling cell cycle checkpoints (Bouchard et al., 2007).

Oncogenic MYC also induces replication stress by driving unscheduled origin firing and nucleotide depletion, contributing to DNA damage and genomic instability (Dominguez-Sola et al., 2007). In normal cells, such stress activates a p53-dependent failsafe mechanism leading to apoptosis or senescence; however, in the context of TP53 mutations, MYC-driven stress supports malignant progression. Targeting MYC directly remains challenging due to its disordered protein structure, but emerging strategies include disruption of MYC-MAX dimerisation, inhibition of MYC transcription or translation, and synthetic lethality approaches (Whitfield et al., 2017).

RAS: A Molecular Switch Governing Proliferative and Survival Pathways

The RAS family of small GTPases (KRAS, NRAS, HRAS) acts as a key signal transduction node downstream of receptor tyrosine kinases (RTKs). Upon growth factor stimulation, guanine nucleotide exchange factors (GEFs) such

as SOS catalyse GDP-GTP exchange, converting RAS to its active GTP-bound state. Activated RAS engages multiple effectors, including the RAF-MEK-ERK and PI3K-AKT-mTOR pathways, which promote cell proliferation, growth, and survival (Cox et al., 2014).

Mutations in RAS genes—particularly KRAS codons 12, 13, and 61—abolish intrinsic GTPase activity or disrupt GAP-mediated inactivation, resulting in constitutive signalling. Oncogenic RAS upregulates cyclin D1 expression and suppresses CDK inhibitors, driving cell cycle progression. Moreover, RAS-induced ERK signalling enhances MYC stability, creating a positive feedback loop that amplifies oncogenic transcriptional programs.

RAS-driven tumours, such as pancreatic ductal adenocarcinoma, colorectal carcinoma, and non-small-cell lung cancer, are notoriously aggressive and refractory to conventional therapies. While direct RAS inhibition has historically been elusive, KRAS G12C inhibitors (e.g., sotorasib) now provide proof-of-concept for allele-specific targeting (Canon et al., 2019). Understanding RAS-driven cell cycle dependencies and co-targeting parallel pathways (e.g., CDK4/6, MEK, or autophagy) represents a promising therapeutic avenue.

Tumour Suppressors in Cell Cycle Control: RB1 and TP53 as Molecular Gatekeepers

RB1: The Retinoblastoma Pathway and G1/S Transition Restriction

The RB1 gene encodes the retinoblastoma protein (pRB), a key regulator of the G1/S checkpoint that functions as a transcriptional repressor by binding to E2F transcription factors. In quiescent and early G1-phase cells, hypophosphorylated pRB forms inhibitory complexes with E2Fs, preventing the transcription of S-phase-promoting genes. Mitogenic stimulation activates CDK4/6-cyclin D complexes, initiating pRB phosphorylation. Hyperphosphorylation by CDK2-cyclin E leads to the dissociation of pRB-E2F complexes, allowing transcriptional activation of genes essential for DNA synthesis and S-phase progression (Burkhart & Sage, 2008).

Loss of RB1 function occurs via diverse mechanisms, including point mutations, deletions, and epigenetic silencing. Biallelic inactivation results in constitutive E2F activity, unchecked S-phase entry, and heightened susceptibility to replication stress. This phenomenon is a hallmark of retinoblastoma, osteosarcoma, and small-cell lung carcinoma. Moreover, RB1 inactivation promotes chromosomal instability by uncoupling cell cycle progression from mitotic fidelity, further exacerbating tumorigenesis (Dick & Rubin, 2013).

Beyond its canonical role in E2F regulation, pRB interacts with chromatin remodels, DNA replication machinery, and apoptotic regulators, underscoring its multifaceted tumour suppressor function. RB-deficient tumours often exhibit compensatory reliance on p53 or CDK2, highlighting potential vulnerabilities for targeted therapy (McClellan & Slack, 2020).

TP53: Guardian of the Genome and Coordinator of Stress Responses

TP53, encoding the p53 protein, is the most frequently mutated tumour suppressor gene in human cancers. p53 integrates signals from DNA damage, hypoxia, and oncogenic stress to regulate transcription of genes involved in cell cycle arrest, apoptosis, senescence, DNA repair, and metabolism. Upon activation, p53 induces CDKN1A (p21), a potent inhibitor of CDK2, which in turn stabilises pRB and enforces G1 arrest (Vousden & Prives, 2009).

In response to genotoxic stress, the ATM/ATR-Chk1/Chk2 signalling cascade phosphorylates p53, stabilising it and preventing MDM2-mediated ubiquitination and degradation. This allows for temporal orchestration of cell cycle arrest, providing a window for DNA repair. If damage is irreparable, p53 promotes apoptosis through transcriptional upregulation of PUMA, NOXA, and BAX, or induction of senescence via p21 and p16 pathways (Horn & Vousden, 2007).

Mutations in TP53 typically result in missense variants within the DNA-binding domain, abolishing transcriptional activity or conferring dominant-negative and gain-of-function properties. These mutant p53 proteins not only fail to induce cell cycle arrest and apoptosis but also promote tumour cell migration, invasion, and metastasis through chromatin remodelling and metabolic reprogramming (Freed-Pastor & Prives, 2012).

Importantly, p53-deficient cancers exhibit synthetic lethality with checkpoint kinase inhibition. Pharmacologic agents targeting WEE1, ATR, and CHK1 pathways are under clinical investigation for selectively eliminating p53-incompetent tumour cells by exacerbating replication stress (Reinhardt & Schumacher, 2012).

Checkpoint Dysregulation and Oncogene-Induced Replication Stress

Disruption of G1/S and Intra-S Phase Checkpoints

In healthy cells, the G1/S checkpoint ensures that damaged or unprepared DNA is not replicated. This restriction is achieved through the coordinated activity of tumour suppressors (e.g., RB1, TP53), checkpoint kinases (ATM/ATR), and CDK inhibitors (e.g., p21, p27). DNA double-strand breaks activate ATM,

whereas replication stress, characterised by stalled replication forks and exposed single-stranded DNA, activates ATR. These kinases phosphorylate and stabilise downstream effectors such as CHK1 and CHK2, resulting in the inhibition of CDC25 phosphatases, suppression of CDK2 activity, and maintenance of RB1 in a hypophosphorylated, growth-suppressive state (Bartek & Lukas, 2007).

In cancer, frequent inactivation of p53, deletion of CDKN2A (encoding p16INK4A and p14ARF), and overexpression of cyclin D1 or CDK4/6 bypass this checkpoint, leading to inappropriate S-phase entry. The consequence is a permissive environment for replication of damaged DNA, enhancing the risk of mutations, chromosomal rearrangements, and genomic instability (Negrini et al., 2010).

Oncogene-Induced Replication Stress: Molecular Drivers and Outcomes

Oncogene activation, particularly of MYC, RAS, and cyclin E, accelerates cell cycle progression and increases replication origin firing. This hyperproliferative state exhausts nucleotide pools, reduces replication fork speed, and leads to frequent fork stalling and collapse. The resulting accumulation of single- and double-stranded DNA breaks triggers chronic activation of the DDR, particularly the ATR-CHK1 pathway, which becomes essential for cell survival under stress (Zeman & Cimprich, 2014).

Replication stress is not merely a byproduct of transformation; it is a driver of genomic instability and tumour heterogeneity. It contributes to chromothripsis, kataegis, and other mutational phenomena frequently observed in cancer genomes. Importantly, while normal cells resolve such stress via transient arrest or apoptosis, cancer cells tolerate replication errors, thus accumulating a mutator phenotype that fuels evolution and therapy resistance (Gaillard et al., 2015).

Checkpoints in G2/M and Mitosis: Balancing Genome Integrity and Survival

The G2/M checkpoint ensures that cells do not enter mitosis with damaged or incompletely replicated DNA. Activation of ATM/ATR and CHK1/CHK2 kinases in G2 leads to inhibition of CDC25C, preventing activation of CDK1-cyclin B and delaying mitotic entry. In TP53-deficient tumours, G2/M checkpoint control is often the last line of defence against propagation of DNA lesions. This reliance creates vulnerability to WEE1 inhibitors, which disrupt CDK1 control and induce mitotic catastrophe (Sloss et al., 2016).

During mitosis, the spindle assembly checkpoint (SAC) monitors the proper attachment of kinetochores to spindle microtubules. Key components—MAD2, BUB1, BUBR1—sequester CDC20 and inhibit the anaphase-promoting complex

(APC/C) until proper alignment is achieved. In cancer, SAC is frequently dysregulated. Either its components are overexpressed (causing mitotic delay and chromosomal instability) or underactive (allowing premature anaphase and aneuploidy) (Kops et al., 2005).

Exploiting Replication Stress and Checkpoint Dependence for Therapy

Cancer cells' dependence on ATR, CHK1, and WEE1 for survival under replicative stress has prompted the development of small-molecule inhibitors targeting these kinases. ATR inhibitors (e.g., berzosertib), CHK1 inhibitors (e.g., prexasertib), and WEE1 inhibitors (e.g., adavosertib) have shown efficacy in preclinical models and early-phase clinical trials, particularly in TP53-deficient or MYC-driven cancers (Lecona & Fernández-Capetillo, 2014). The combination of these inhibitors with DNA-damaging agents or immune checkpoint inhibitors may enhance therapeutic response.

Future strategies will likely involve precision profiling of checkpoint dependencies using functional genomics and real-time imaging of replication dynamics. Understanding how tumours adapt to chronic checkpoint inhibition will also be crucial to overcoming resistance mechanisms.

Chromosomal Instability and Spindle Checkpoint Tolerance in Tumor Evolution

Chromosomal Instability: Mechanisms and Consequences

Chromosomal instability (CIN) refers to an increased rate of chromosomal missegregation and structural alterations during cell division. It is a hallmark of most solid tumours and haematological malignancies and manifests as both numerical changes (aneuploidy) and structural rearrangements (translocations, deletions, duplications). CIN arises from defects in mitotic spindle assembly, kinetochore-microtubule attachments, centrosome amplification, and cohesion fatigue (Bakhoum & Compton, 2012).

Aberrant mitotic progression in CIN-positive cells often stems from weakened or overridden spindle assembly checkpoint (SAC) signals. Incomplete kinetochore attachments, if uncorrected, can lead to lagging chromosomes, chromatin bridges, and micronuclei formation. These structures are prone to nuclear envelope rupture and catastrophic DNA fragmentation, as seen in chronotherapies, a phenomenon where a single mitotic error can result in tens to hundreds of rearrangements in a localised genomic region (Zhang et al., 2015).

Although high levels of CIN are associated with tumour heterogeneity and adaptability, they also pose fitness costs. Excessive CIN can lead to mitotic catastrophe or immune detection via cytosolic DNA sensing pathways like cGAS-STING. Thus, tumours maintain CIN within a tolerable range to balance adaptability with viability (Santaguida & Amon, 2015).

Tolerance of Spindle Assembly Checkpoint Disruption

The SAC ensures temporal fidelity in mitosis by delaying anaphase onset until all kinetochores are bi-oriented on the mitotic spindle. Core SAC components—including MAD1, MAD2, BUB1, BUB3, and BUBR1—form a mitotic checkpoint complex that inhibits CDC20, a co-activator of the APC/C. In cancer, SAC regulators are frequently overexpressed or mutated, leading to prolonged mitosis or premature anaphase, respectively (Ryan et al., 2012).

Paradoxically, SAC overexpression may reflect a compensatory adaptation to other mitotic defects. For instance, increased MAD2 levels correlate with enhanced tolerance to microtubule poisons but also with elevated aneuploidy and poor prognosis in several cancers. Conversely, partial loss of SAC function reduces mitotic duration and increases segregation errors, contributing to the generation of diverse karyotypes from a single progenitor clone (Li & Murray, 2011).

Targeting SAC regulators is an emerging therapeutic strategy. Inhibitors of MPS1 (TTK), a kinase essential for SAC activation, induce premature mitotic exit and chromosome missegregation in cancer cells, pushing CIN beyond sustainable limits. Clinical trials of MPS1 inhibitors are ongoing in tumours with high baseline CIN or TP53 deficiency (Tardif et al., 2021).

CIN as a Driver of Therapy Resistance and Immune Modulation

CIN-driven tumour evolution facilitates adaptation to cytotoxic therapies and targeted agents. Subclonal karyotypic heterogeneity allows for rapid selection of resistant populations. Moreover, CIN influences immune recognition: micronuclei-derived DNA activates the cGAS-STING axis, leading to interferon responses that can either promote immune surveillance or drive immune evasion depending on the context (Mackenzie et al., 2017).

CIN also creates opportunities for synthetic lethality. For example, cells with elevated replication stress and chromosomal missegregation depend heavily on spindle checkpoint proteins and mitotic DNA damage response pathways. Exploiting these dependencies via dual targeting of SAC components and replication stress mediators holds promise in high-CIN tumours.

References

Bakhoum, S.F. and Compton, D.A., 2012. Chromosomal instability and cancer: a complex relationship with therapeutic potential. *Journal of Clinical Investigation*, 122(4), pp.1138–1143. https://doi.org/10.1172/JCI59954

Bartek, J. and Lukas, J., 2007. DNA damage checkpoints: from initiation to recovery or adaptation. *Current Opinion in Cell Biology*, 19(2), pp.238–245. https://doi.org/10.1016/j.ceb.2007.02.009

Burkhart, D.L. and Sage, J., 2008. Cellular mechanisms of tumour suppression by the retinoblastoma gene. *Nature Reviews Cancer*, 8(9), pp.671–682. https://doi.org/10.1038/nrc2399

Canon, J. et al., 2019. The clinical KRAS(G12C) inhibitor AMG 510 drives anti-tumour immunity. *Nature*, 575(7781), pp.217–223. https://doi.org/10.1038/s41586-019-1694-1

Cox, A.D. et al., 2014. Drugging the undruggable RAS: Mission possible? *Nature Reviews Drug Discovery*, 13(11), pp.828–851. https://doi.org/10.1038/nrd4389

Dang, C.V., 2012. MYC on the path to cancer. *Cell*, 149(1), pp.22–35. https://doi.org/10.1016/j.cell.2012.03.003

Dick, F.A. and Rubin, S.M., 2013. Molecular mechanisms underlying RB protein function. *Nature Reviews Molecular Cell Biology*, 14(5), pp.297–306. https://doi.org/10.1038/nrm3567

Dominguez-Sola, D. et al., 2007. Non-transcriptional control of DNA replication by c-Myc. *Nature*, 448(7152), pp.445–451. https://doi.org/10.1038/nature05902

Freed-Pastor, W.A. and Prives, C., 2012. Mutant p53: one name, many proteins. *Genes & Development*, 26(12), pp.1268–1286. https://doi.org/10.1101/gad.190678.112

Gaillard, H., García-Muse, T. and Aguilera, A., 2015. Replication stress and cancer. *Nature Reviews Cancer*, 15(5), pp.276–289. https://doi.org/10.1038/nrc3916

Hanahan, D. and Weinberg, R.A., 2011. Hallmarks of cancer: the next generation. *Cell*, 144(5), pp.646–674. https://doi.org/10.1016/j.cell.2011.02.013

Horn, H.F. and Vousden, K.H., 2007. Coping with stress: multiple ways to activate p53. *Oncogene*, 26(9), pp.1306–1316. https://doi.org/10.1038/sj.onc.1210263

Kops, G.J., Weaver, B.A. and Cleveland, D.W., 2005. On the road to cancer: aneuploidy and the mitotic checkpoint. *Nature Reviews Cancer*, 5(10), pp.773–785. https://doi.org/10.1038/nrc1714

Lawson, D.A. et al., 2020. Tumour heterogeneity and metastasis at single-cell resolution. *Nature Cell Biology*, 22(3), pp.294–307. https://doi.org/10.1038/s41556-020-0472-5

Lecona, E. and Fernández-Capetillo, O., 2014. Replication stress and cancer: it takes two to tango. *Experimental Cell Research*, 329(1), pp.26–34. https://doi.org/10.1016/j.yexcr.2014.09.019

Li, R. and Murray, A.W., 2011. Feedback control of mitosis in budding yeast. *Cell*, 145(3), pp.393–405. https://doi.org/10.1016/j.cell.2011.03.044

Mackenzie, K.J. et al., 2017. cGAS surveillance of micronuclei links genome instability to innate immunity. *Nature*, 548(7668), pp.461–465. https://doi.org/10.1038/nature23449

Malumbres, M. and Barbacid, M., 2009. Cell cycle, CDKs and cancer: a changing paradigm. *Nature Reviews Cancer*, 9(3), pp.153–166. https://doi.org/10.1038/nrc2602

McClellan, K.A. and Slack, R.S., 2020. Specific inactivation of Rb in the nervous system: new insights into disease. *Trends in Neurosciences*, 43(5), pp.286–298. https://doi.org/10.1016/j.tins.2020.02.001

Morgan, D.O., 2007. *The Cell Cycle: Principles of Control*. Oxford: Oxford University Press.
Negrini, S., Gorgoulis, V.G. and Halazonetis, T.D., 2010. Genomic instability—an evolving hallmark of cancer. *Nature Reviews Molecular Cell Biology*, 11(3), pp.220–228. https://doi.org/10.1038/nrm2858
Nijman, S.M., 2011. Synthetic lethality: general principles, utility and detection using genetic screens in human cells. *FEBS Letters*, 585(1), pp.1–6. https://doi.org/10.1016/j.febslet.2010.11.024
Reinhardt, H.C. and Schumacher, B., 2012. The p53 network: cellular and systemic DNA damage responses in aging and cancer. *Trends in Genetics*, 28(3), pp.128–136. https://doi.org/10.1016/j.tig.2011.12.004
Ryan, S.D. et al., 2012. Up-regulation of the mitotic checkpoint component Mad1 causes chromosomal instability and resistance to microtubule poisons. *Proceedings of the National Academy of Sciences*, 109(33), pp.E2205–E2214. https://doi.org/10.1073/pnas.1201911109
Santaguida, S. and Amon, A., 2015. Short- and long-term effects of chromosome mis-segregation and aneuploidy. *Nature Reviews Molecular Cell Biology*, 16(9), pp.576–590. https://doi.org/10.1038/nrm4045
Sherr, C.J. and McCormick, F., 2002. The RB and p53 pathways in cancer. *Cancer Cell*, 2(2), pp.103–112. https://doi.org/10.1016/S1535-6108(02)00102-2
Sloss, O., Topham, C., Diez, M. and Taylor, S., 2016. Cancer therapy: the long and winding road to mitotic catastrophe. *Trends in Cell Biology*, 26(10), pp.728–739. https://doi.org/10.1016/j.tcb.2016.05.007
Taub, R. et al., 1982. Translocation of the c-myc gene into the immunoglobulin heavy chain locus in human Burkitt lymphoma and murine plasmacytoma cells. *Proceedings of the National Academy of Sciences*, 79(24), pp.7837–7841. https://doi.org/10.1073/pnas.79.24.7837
Tardif, K.D. et al., 2021. Targeting MPS1 sensitizes basal-like breast cancer to antimitotic agents. *Cancer Research*, 81(1), pp.128–139. https://doi.org/10.1158/0008-5472.CAN-20-1904
Vousden, K.H. and Prives, C., 2009. Blinded by the light: the growing complexity of p53. *Cell*, 137(3), pp.413–431. https://doi.org/10.1016/j.cell.2009.04.037
Whitfield, J.R. and Soucek, L., 2017. Tumor microenvironment: becoming sick of Myc. *Cellular and Molecular Life Sciences*, 74(9), pp.1759–1765. https://doi.org/10.1007/s00018-016-2412-7
Zeman, M.K. and Cimprich, K.A., 2014. Causes and consequences of replication stress. *Nature Cell Biology*, 16(1), pp.2–9. https://doi.org/10.1038/ncb2897
Zhang, C.Z. et al., 2015. Chromothripsis from DNA damage in micronuclei. *Nature*, 522(7555), pp.179–184. https://doi.org/10.1038/nature14493