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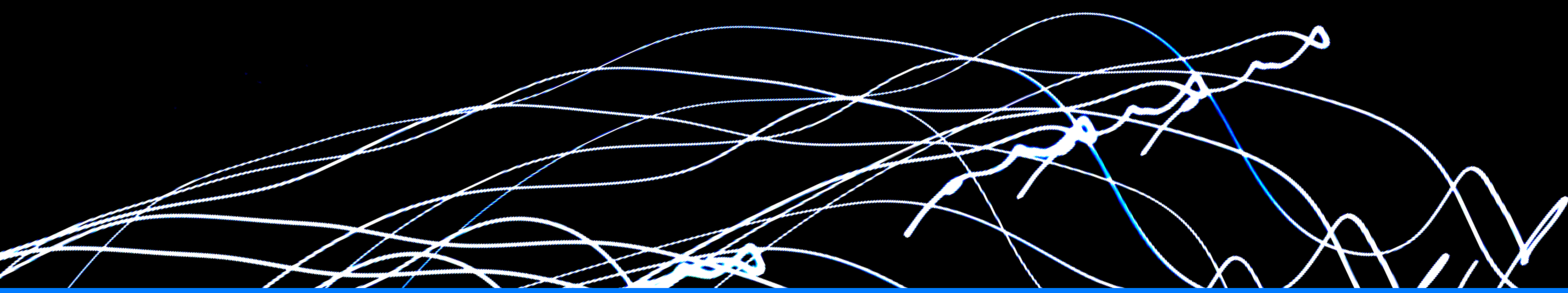

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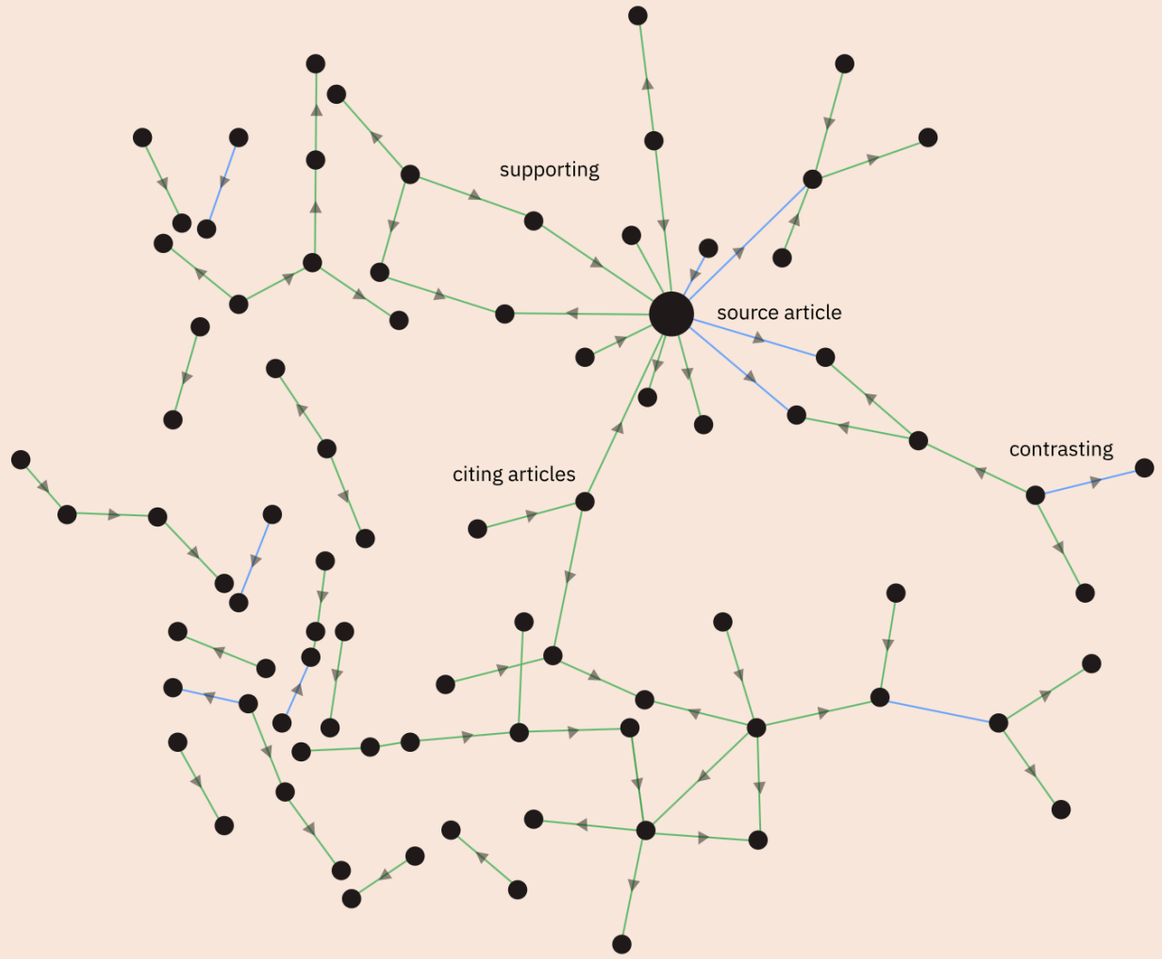

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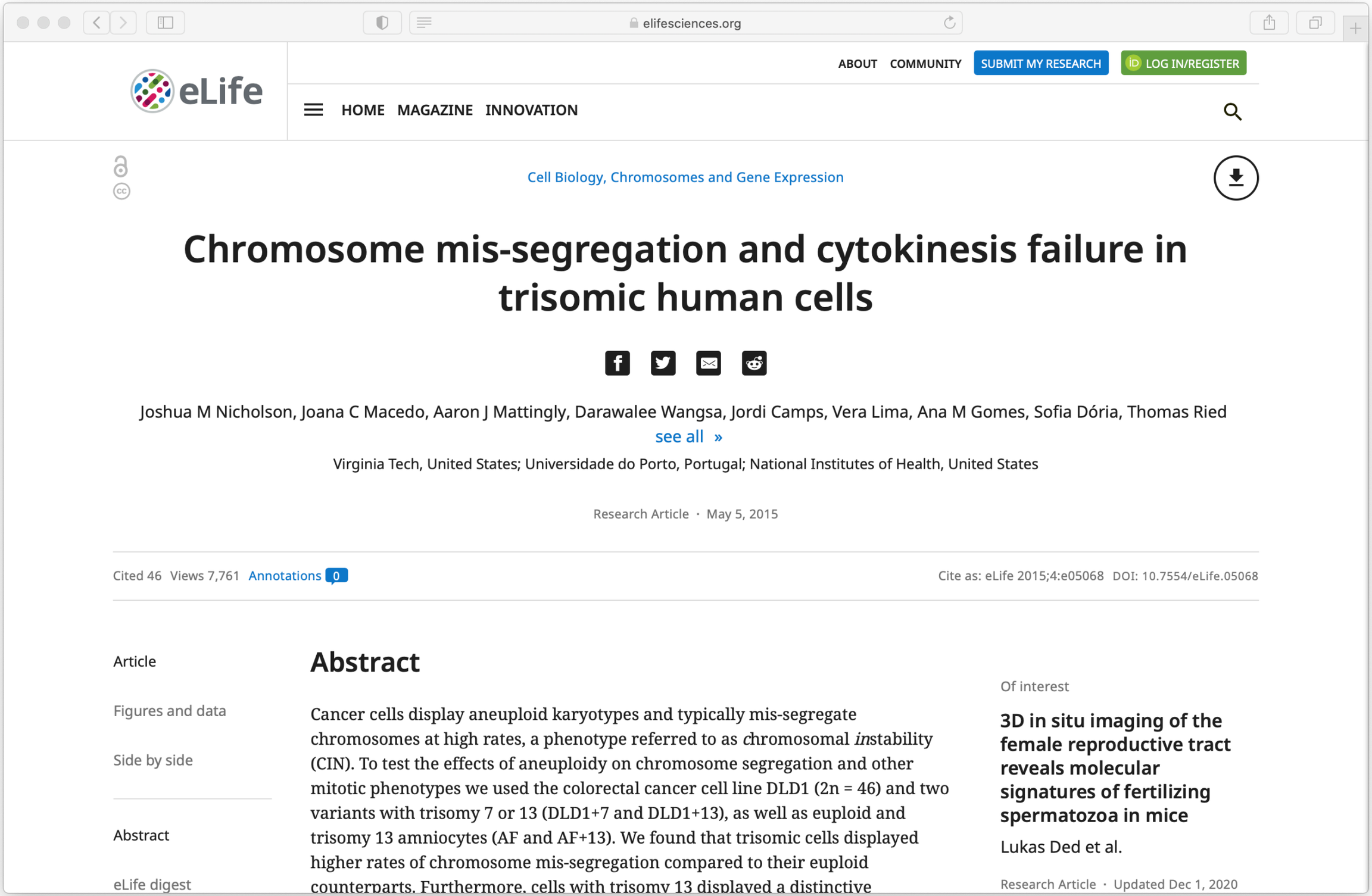
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Abstract
Cancer cells display aneuploid karyotypes and typically mis-segregate chromosomes at high rates, a phenotype referred to as chromosomal instability (CIN). To test the effects of aneuploidy on chromosome segregation and other mitotic phenotypes we used the colorectal cancer cell line DLD1 (2n = 46) and two variants with trisomy 7 or 13 (DLD1+7 and DLD1+13), as well as euploid and trisomy 13 amniocytes (AF and AF+13). We found that trisomic cells displayed higher rates of chromosome mis-segregation compared to their euploid counterparts. Furthermore, cells with trisomy 13 displayed a distinctive
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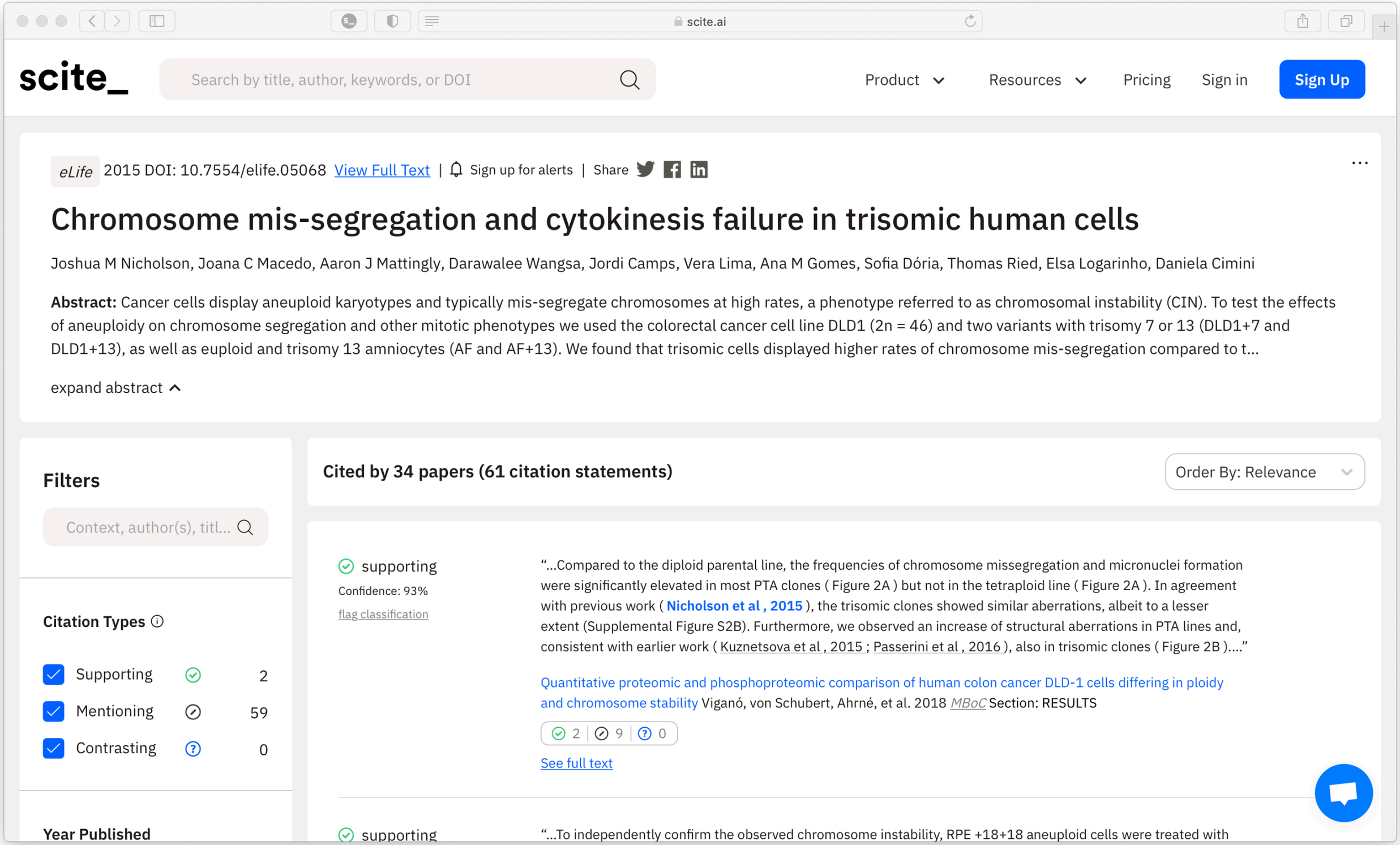

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duplication cycle (Holland and Cleveland, 2009; Thompson and Compton, 2010).

Studies carried out primarily in yeast and mammalian cell lines have shown that aneuploidy comes with a fitness cost. Aneuploid cells typically grow slower (McCoy *et al.*, 1974; Torres *et al.*, 2007; Williams *et al.*, 2008; Tang *et al.*, 2011; Siegel and Amon, 2012; Stingele *et al.*, 2012) and suffer from replication stress that leads to DNA damage and gene mutation (Janssen *et al.*, 2011; Crasta *et al.*, 2012; Santaguida and Amon, 2015a; Passerini *et al.*, 2016; Ly and Cleveland, 2017). Also, both in vitro engineered aneuploid cells and chromosomally unstable cancer cells display gene expression patterns (Sheltzer, 2013) reminiscent of stress responses first described in yeast (Gasch, 2007). Accordingly, aneuploid cells were found to show increased sensitivity toward compounds inducing energy stress and proteotoxic stress (Tang *et al.*, 2011). In nontransformed cells, chromosome missegregation generally leads to p53-dependent cell cycle arrest and, ultimately, cell death (Li *et al.*, 2010; Thompson and Compton, 2010; Uetake and Sluder, 2010; Janssen *et al.*, 2011; Lambrus *et al.*, 2016). Yet, despite this fitness cost, severe aneuploidy and CIN are hallmarks of human cancers (Hanahan and Weinberg, 2011; Holland and Cleveland, 2012; Funk *et al.*, 2016; De Braekeleer *et al.*, 2017). They contribute to increased transformative potential (Paulsson and Johansson, 2007; Weaver *et al.*, 2007) and correlate with poor prognosis (McGranahan *et al.*, 2012). To resolve this apparent conundrum, it is generally argued that aneuploidy and CIN result in deregulated gene expression, which then confers a selective advantage during the evolution of a tumor in a changing microenvironment (Baek *et al.*, 2009; Pavelka *et al.*, 2010; Kwon-Chung and Chang, 2012; Yona *et al.*, 2012). As one example supporting this notion, DLD-1 cells engineered to carry single-chromosome aneuploidies were found to have a selective advantage over diploid control cells when cultured under non-standard conditions, such as serum starvation, drug treatment, or hypoxia (Rutledge *et al.*, 2016). Such observations, as well as data obtained in tumor models, strongly support the hypothesis that aneuploidy is not a by-product of cell transformation but, when present at appropriate levels, contributes to tumor development (Hanks *et al.*, 2004; Holland and Cleveland, 2012; Davoli *et al.*, 2013).

Aneuploidy in cancer cells may arise when diploid progenitors gain or lose individual chromosomes. However, chromosome loss is not well tolerated in diploid cells (Alvaro *et al.*, 2006; Anders *et al.*, 2009). Moreover, cancer cells often carry near-tetraploid chromosome numbers, indicative of whole genome duplication events (Zack *et al.*, 2013). This suggests that aneuploid cancer cells often derive from tetraploid intermediates (Cowell and Wigley, 1980; Mayer and Aguilera, 1990; Storchova and Pellman, 2004; Storchova and Kuffer, 2008; Holland and Cleveland, 2012). Considering that tetraploidization creates redundancy in chromosome content, it is expected to protect descendant aneuploid cells from the negative effects of haploinsufficiency (Shackney *et al.*, 1989; Storchova and Pellman, 2004; Ganem and Pellman, 2007; Thompson and Compton, 2010; Dewhurst *et al.*, 2014).

Aneuploidy has traditionally been ascribed to defects in mitotic spindle organization and/or dysfunction of the spindle assembly checkpoint (Wang *et al.*, 2007; Kops *et al.*, 2005). However, although mutations in spindle checkpoint genes can indeed cause aneuploidy (Hanks *et al.*, 2004; Yost *et al.*, 2017), such mutations have not been commonly observed in cancers (Cahill *et al.*, 1999; Haruki *et al.*, 2001). Deregulated expression of essential regulators of chromosome segregation and cell division has been observed in cancers with high degrees of aneuploidy and, accordingly, a CIN marker signature (CIN70) was proposed (Carter *et al.*, 2006). However, subsequent studies argued that this CIN signature reflects altered proliferation rate rather than chromosome missegregation (Venet *et al.*, 2011; Sheltzer, 2013; Buccitelli *et al.*, 2017). Thus, a specific cellular response to CIN has not yet been identified.

Here we established a set of transformed cancer cell lines of isogenic origin but differing in chromosome content and propensity to chromosome missegregation. To determine the effects of gains in chromosome mass *versus* CIN on protein expression and phosphorylation, we subjected the different cell lines to extensive proteomic and phosphoproteomic analyses. We found that proteomic changes in response to CIN are similar to those observed in response to tetraploidy and are more readily detectable at the level of protein phosphorylation than at the level of protein expression. Furthermore, our results indicate that large gains in chromosome number, as caused by tetraploidization, trigger widespread responses in protein expression and phosphorylation patterns, lending support to the notion that an initial genome doubling event can set the stage for survival and propagation of descendent aneuploid tumor cells.

RESULTS

Establishment of DLD-1–derived cell lines differing in ploidy and aneuploidy

Chromosome gains or losses result in massive changes in gene expression (Lyle *et al.*, 2004; Upender *et al.*, 2004; Stingele *et al.*, 2012), and protein expression patterns in cancer cell lines are known to reflect tissue origin, a priori making it difficult to identify a proteomic signature attributable to CIN. This notwithstanding, we subjected a panel of human cell lines to a proteomic quantification based on multiplexed tandem mass tag (TMT) labeling, a method of choice for achieving high proteome coverage in multiple samples and within a reasonable time frame (Thompson *et al.*, 2003; Ahrne *et al.*, 2016)(Supplemental Figure S1A and Supplemental Table S1). This panel included seven karyotypically stable (nonCIN) and unstable (CIN) cancer cell lines originating from different tumor tissues (Gascoigne and Taylor, 2008) and the immortalized retinal cell line hTERT. In line with previous data (Gascoigne and Taylor, 2008), we found that differences in global protein expression patterns were too profound to allow a distinction between CIN and karyotypically stable (nonCIN) cell lines through hierarchical cluster analysis (Supplemental Figure S1B). Nevertheless, this pilot study showed that our proteomics approach allowed for reliable quantification of thousands of proteins in each cell line.

To reduce interline variation due to tissue origin, we next used the diploid colon cancer cell line DLD-1 to generate descendant lines differing in karyotype. DLD-1 cells show microsatellite instability (MIN) but proliferate in a near-diploid state (Lengauer *et al.*, 1997). As DLD-1 cells are deficient in p53, tetraploid derivatives can readily be established through inhibition of cytokinesis (Dresdopoulos *et al.*, 2014). This afforded a syngeneic pair of stable diploid and tetraploid cells (Figure 1A). Starting with a culture of tetraploid DLD-1 cells, we then used single cell fluorescence-activated sorting (FACS) to isolate spontaneously arising aneuploid descendants. This provided us with four different PTA clones, specifically three near-triploid lines and one near-tetraploid line (Figure 1B). Finally, we applied microcell-mediated chromosome transfer (Stingele *et al.*, 2012) to the parental diploid DLD-1 culture and obtained two viable trisomic clones carrying three copies of chromosome 7 (Tr 7) (Figure 1B). For all cell lines, DNA content was confirmed by chromosome counting (Figure 1C) and chromosome painting (Supplemental Figure S2A). This collection of isogeneic cell lines set the stage for analyzing chromosomally stable diploid,

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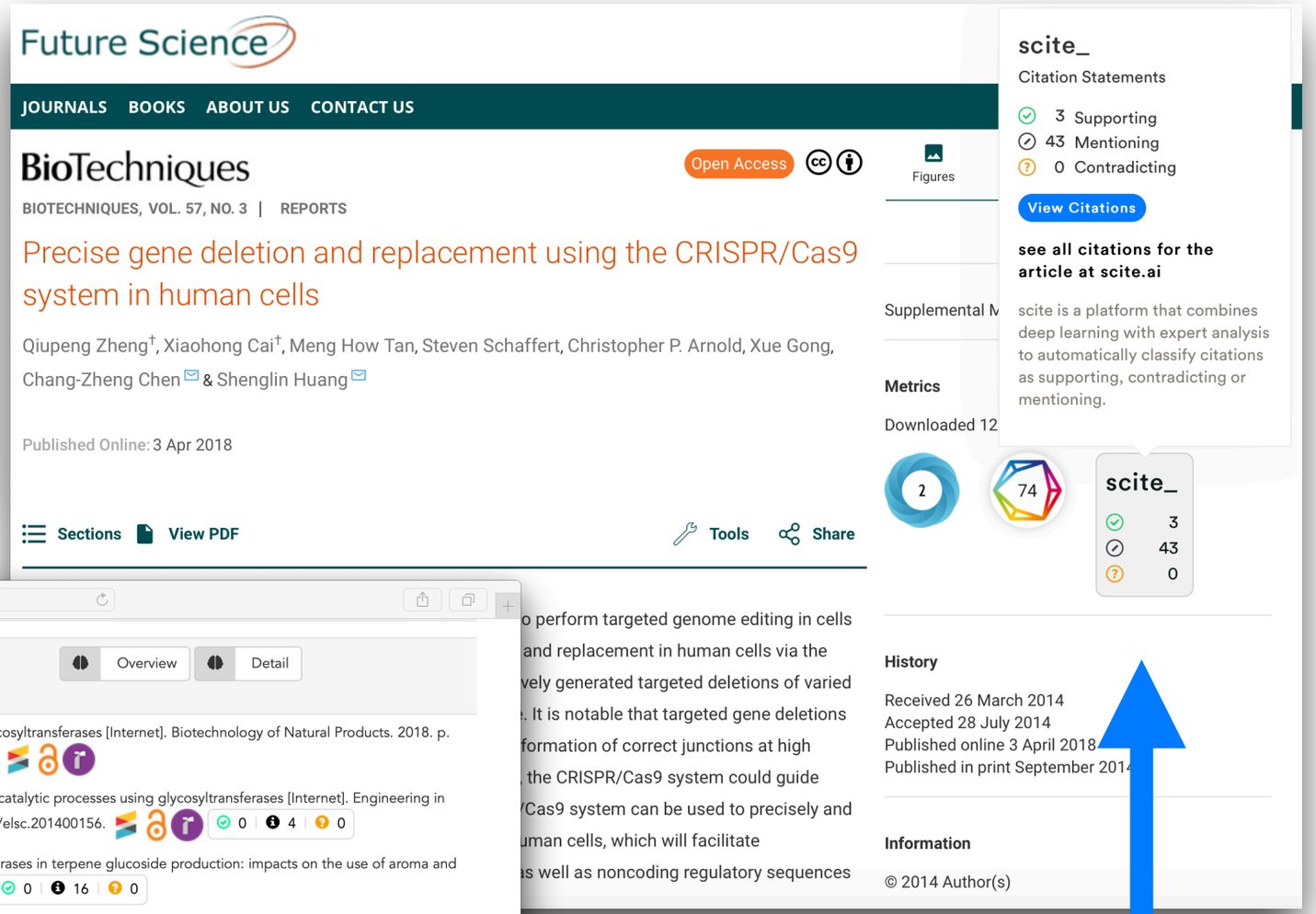

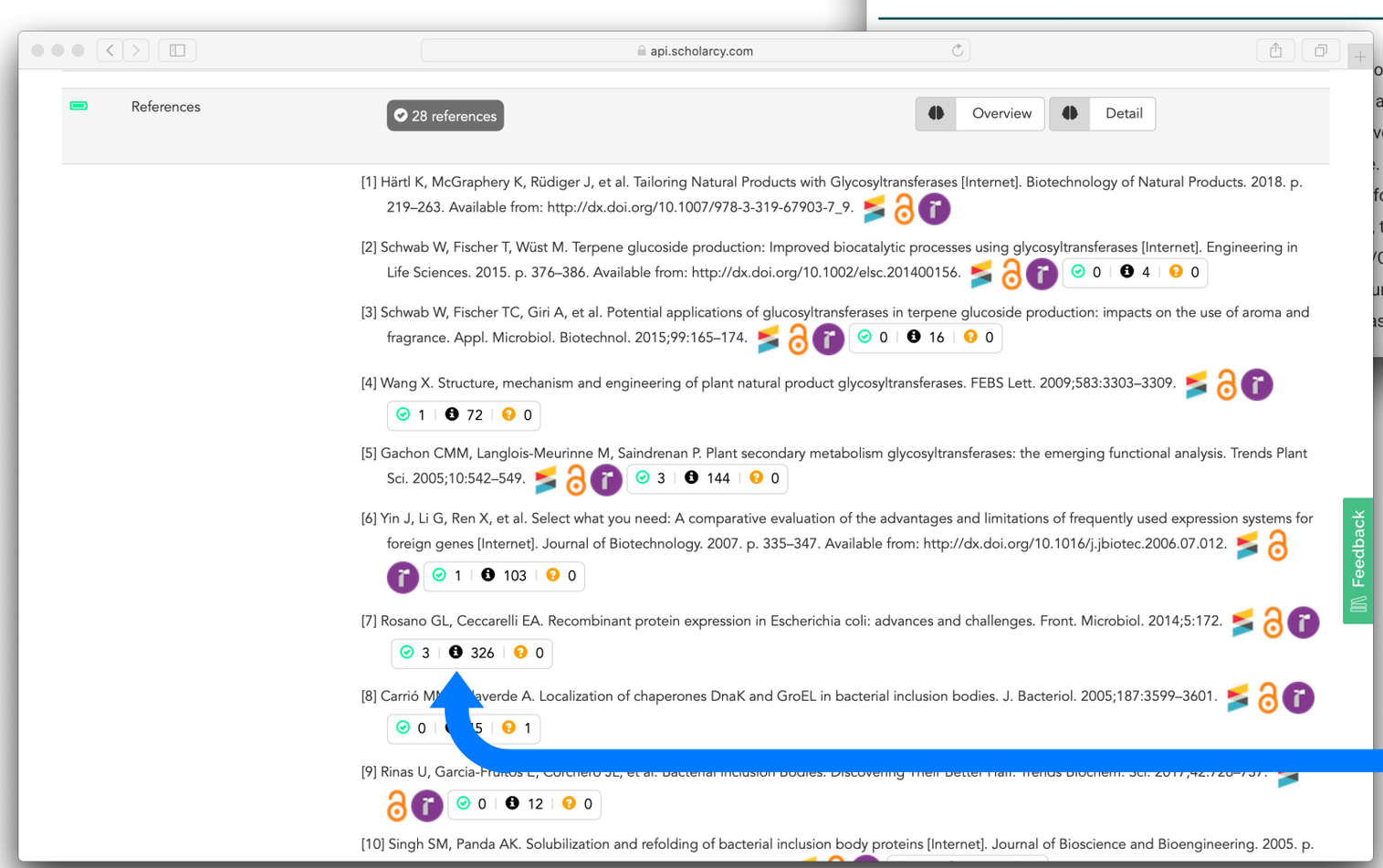

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ARTICLE

Epigenetic silencing of miR-483-3p promotes acquired gefitinib resistance and EMT in EGFR-mutant NSCLC by targeting integrin β3

Jinnan Yue[1] · Dacheng Lv[1] · Caiyun Wang[1] · Ling Li[1] · Qingnan Zhao[1] · Hongzhuan Chen[1] · Lu Xu[1]

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Abstract
All lung cancers patients with epidermal growth factor receptor (EGFR) mutation inevitably develop acquired resistance to EGFR tyrosine kinase inhibitors (TKI). In up to 30% of cases, the mechanism underlying acquired resistance remains unknown. MicroRNAs (miRNAs) is a group of small non-coding RNAs commonly dysregulated in human cancers and have been implicated in therapy resistance. The aim of this study was to understand the roles of novel miRNAs in acquired EGFR TKI resistance in EGFR-mutant non-small cell lung cancer (NSCLC). Here, we reported the evidence of miR-483-3p silencing and epithelial-to-mesenchymal transition (EMT) phenotype in both in vitro and in vivo EGFR-mutant NSCLC models with acquired resistance to gefitinib. In those tumor models, forced expression of miR-483-3p efficiently increased sensitivity of gefitinib-resistant lung cancer cells to gefitinib by inhibiting proliferation and promoting apoptosis. Moreover, miR-483-3p reversed EMT and inhibited migration, invasion, and metastasis of gefitinib-resistant lung cancer cells. Mechanistically, miR-483-3p directly targeted integrin β3, and thus repressed downstream FAK/Erk signaling pathway. Furthermore, the silencing of miR-483-3p in gefitinib-resistant lung cancer cells was due to hypermethylation of its own promoter. Taken together, our data identify miR-483-3p as a promising target for combination therapy to overcome acquired EGFR TKI resistance in EGFR-mutant NSCLC.

INTRODUCTION

EGFR tyrosine kinase inhibitors (TKI) including gefitinib and erlotinib have demonstrated dramatic efficacy in non-small cell lung cancer (NSCLC) patients with EGFR-activating mutation [1]. In general, activating EGFR mutations are more commonly observed in non-smoking, female, Asian patients with adenocarcinoma histology, which is one of the most common histological subtypes of NSCLC. Despite impressive initial response, almost all patients eventually have a relapse due to the occurrence of acquired resistance. Several mechanisms leading to acquired resistance have been demonstrated, including EGFR T790M mutation, MET amplification, PIK3CA mutation, AXL activation, small cell lung cancer (SCLC) transformation, or acquiring an epithelial-to-mesenchymal transition (EMT) phenotype [2–7]. To note, these mechanisms of acquired resistance can take place together in different subclones of the same tumor at the same time. However, the mechanisms remain unknown in ~ 30% of cases.

MicroRNAs (miRNA) are a class of small non-coding, endogenous RNAs of 21–25 nucleotides in length, which repress target genes expression by directly binding to the 3′-untranslated region (UTR) of target gene mRNAs and

These authors contributed equally: Jinnan Yue and Dacheng Lv

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Epigenetic silencing of miR-483-3p promotes acquired gefitinib resistance and EMT in EGFR-mutant NSCLC by targeting integrin β3

Jinnan Yue, Dacheng Lv, Caiyun Wang, Ling Li, Qingnan Zhao, Hongzhuan Chen, Lu Xu

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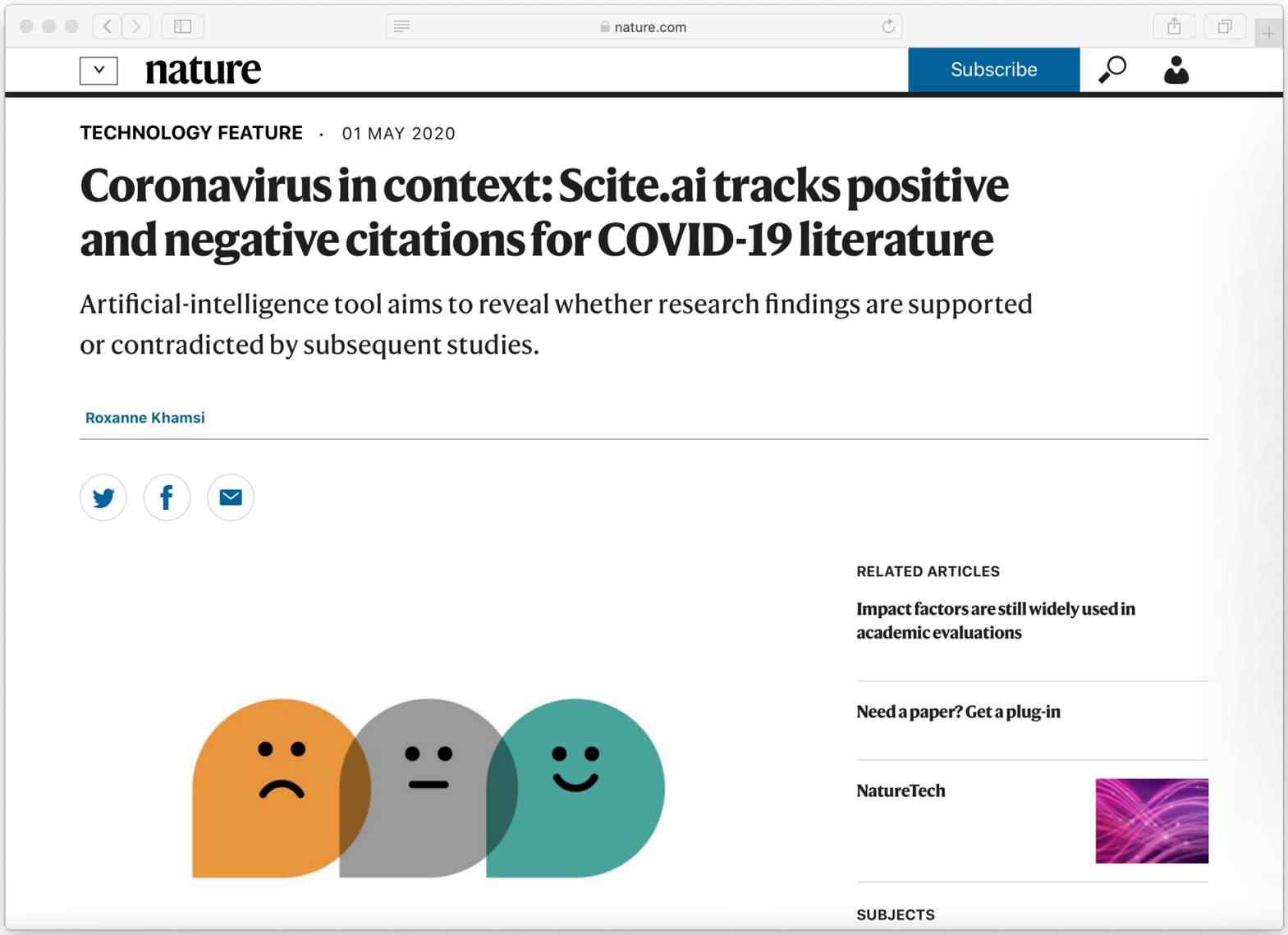

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