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Horizontal DNA Transfer in Human Cells: How Genomic Instability Sends Chromosomal Fragments Across Tunneling Nanotubes to Reprogram Neighbors

Genetics * Molecular & Cellular Biology * Health

For more than a century, mammalian cell biology has rested on the premise that somatic cells inherit nuclear DNA strictly vertically from mother cell to daughter cell during mitosis. A landmark study in Cell by researchers at UT Southwestern Medical Center overturns this boundary -- demonstrating that when human cells suffer chromosomal damage or mitotic errors, they encapsulate megabase-scale genomic fragments into cytoplasmic micronuclei and traffic them directly through actin- and tubulin-rich tunneling nanotubes into neighboring cells, where the foreign DNA enters the host nucleus, integrates into chromosomes, and heritably alters cellular behavior [1, 2] .

1. Overturning the Dogma of Strict Somatic Cell Autonomy

In prokaryotic microbiology, horizontal gene transfer (HGT) is a foundational engine of adaptation. Bacteria routinely exchange plasmids, transposons, and chromosomal islands across species boundaries via conjugation pili, bacteriophage transduction, and natural transformation, allowing a single antibiotic-resistance cassette to sweep through a polymicrobial community within hours [3, 5] . In multicellular eukaryotes -- and particularly in human somatic tissues -- the nuclear genome has traditionally been viewed as a sealed, cell-autonomous vault. Under classical Mendelian and somatic clonal theory, a human epithelial cell, fibroblast, or tumor cell can pass its nuclear genetic blueprint only vertically to its own mitotic progeny; if a cell acquires an adaptive or oncogenic mutation, that allele spreads through a tissue solely by out-proliferating surrounding clones [1, 2] .

A comprehensive investigation published in Cell (Vol. 189, pp. 4548-4561) by Elizabeth G. Maurais, Dr. Peter Ly, and colleagues at the Children's Medical Center Research Institute (CRI) at UT Southwestern Medical Center demonstrates that human somatic cells possess a direct, regulated capacity for intercellular genomic DNA transfer [1, 2] . Rather than remaining strictly isolated within individual nuclei, large segments of human chromosomal DNA -- ranging from tens of kilobases to multi-megabase chromosome arms -- can escape from genomically unstable donor cells, cross physical cytoplasmic bridges into adjacent recipient cells, incorporate into the recipient's nuclear genome during subsequent cell divisions, and drive long-term transcriptional and behavioral reprogramming [1, 2] .

By combining dual-color fluorescence live-cell imaging, chromosome-specific CRISPR-Cas9 cleavage systems, single-cell whole-genome sequencing, and antibiotic-selection co-culture assays, the UT Southwestern team tracked the complete life cycle of horizontally transferred human DNA from its origin in a damaged donor nucleus to its functional expression in a genetically distinct host cell [1] .

2. The Trigger: Mitotic Errors, Centromere Disruption & Cytoplasmic Micronuclei

Under homeostatic conditions, intact chromosomes are sequestered inside the primary nucleus by the double-membraned nuclear envelope , reinforced on its inner surface by the nuclear lamina (lamins A/C and B1/B2) and gated by nuclear pore complexes [1, 4] . How, then, does a megabase-scale segment of human genomic DNA become untethered and available for export to a neighboring cell? Maurais and Ly discovered that intercellular DNA transfer is specifically triggered by genomic instability -- specifically events that missegregate chromosomes during mitosis and trap nuclear DNA within cytoplasmic micronuclei [1, 2] .

When a dividing human cell experiences DNA double-strand breaks (induced by ionizing radiation, radiomimetic drugs, or targeted endonucleases) or mitotic spindle defects (such as merotelic kinetochore attachments or inhibition of the spindle assembly checkpoint kinase MPS1 and centromeric motor CENP-E), two classes of chromosomal bodies frequently lag behind at the metaphase plate during anaphase [1, 4] :

* Acentric Chromosome Fragments: Chromosome arms severed from their centromere by a double-strand break lack a kinetochore and cannot attach to spindle microtubules, leaving them stranded in the cleavage furrow as the daughter nuclei reform.

* Whole Lagging Chromosomes: Intact chromosomes with improperly oriented microtubule attachments fail to migrate poleward in time to join the main telophase chromatin mass.

As the cell exits mitosis into G1 phase, these stranded chromosomal elements recruit their own miniature nuclear envelopes, forming spatially isolated satellite structures in the cytoplasm termed micronuclei [1, 4] . Crucially, whereas the primary nucleus is mechanically anchored near the cell center by the LINC (Linker of Nucleoskeleton and Cytoskeleton) complex, micronuclei are smaller (typically 1 to 3 um in diameter), assemble defective nuclear lamina networks depleted of lamin B1, and move freely through the peripheral cytoplasm along cytoskeletal tracks [1, 4] .

To test whether micronucleation directly gates horizontal DNA transfer, the researchers engineered donor human cells carrying a selectable genetic marker (such as a blasticidin- or puromycin-resistance cassette paired with a fluorescent reporter) integrated at a specific chromosomal locus -- for example, on the Y chromosome or a defined autosome [1] . When donor cells divided normally with intact chromosomes, co-culturing them with genetically distinct recipient cells yielded virtually zero transfer of the marker. However, when the team selectively induced micronucleation of the marker-bearing chromosome -- either by transient centromere inactivation, targeted CRISPR-Cas9 cleavage proximal to the centromere, or pharmacological mitotic perturbation -- the frequency of recipient cells acquiring and expressing the donor genomic locus surged by orders of magnitude [1, 2] .

3. The Conduit: Actin-Tubulin Tunneling Nanotubes vs. Extracellular Vesicles

Once a chromosomal fragment is packaged into a cytoplasmic micronucleus, how does it cross the plasma membrane barrier between two intact human cells? Prior literature had explored whether dying cells release fragmented cell-free DNA (cfDNA) into the

extracellular fluid via apoptotic bodies or small extracellular vesicles (exosomes and microvesicles, 40-1,000 nm in diameter) [3, 6] . However, Maurais and Ly found that conditioned medium harvested from donor cells -- or co-cultures separated by semi-permeable Transwell membranes that block physical cell-to-cell contact while permitting free diffusion of soluble DNA and extracellular vesicles -- failed to produce heritable genomic transfer in recipient cells [1, 2] .

Instead, high-resolution time-lapse confocal microscopy revealed that intercellular chromosome transfer requires direct physical cell-to-cell contact mediated by tunneling nanotubes (TNTs) [1, 2] . First described by Rustom and Gerdes in 2004, tunneling nanotubes are ultrafine, open-ended membranous conduits (typically 50 to 700 nm in width and 10 to over 100 um in length) that hover above the substratum and connect the cytoplasm of two cells in three-dimensional space [5, 7] .

| Biophysical & Functional Parameter | | Tunneling Nanotubes (TNTs) -- Direct Cytoplasmic Conduits | | Small Extracellular Vesicles (Exosomes / Microvesicles) | | Apoptotic Bodies & Cell-Free DNA (cfDNA) Uptake | | Bacterial Conjugation (Prokaryotic Benchmark) |

| Structural Architecture | | Continuous plasma-membrane bridge reinforced by F-actin & alpha/beta-tubulin microtubules | | Lipid-bilayer nanovesicles (40-250 nm exosomes; 100-1,000 nm ectosomes) | | Membrane blebs (1-5 um) & nucleosome-bound linear fragments (~167 bp) | | Type IV secretion system (T4SS) protein pilus & relaxosome pore |

| Contact Requirement | | Mandatory direct cell-to-cell contact (blocked by Transwell filters) | | Contact-independent (diffuses across extracellular matrix & biofluids) | | Contact-independent (phagocytosis or scavenger-receptor endocytosis) | | Direct cell-to-cell contact via conjugative pilus retraction |

| Primary Nucleic Acid Cargo | | Intact micronuclei & multi-megabase chromosomal fragments (+ mitochondria) | | MicroRNAs (miRNAs), mRNAs, lncRNAs & short dsDNA fragments (<2-10 kb) | | CAD-cleaved oligonucleosomal DNA ladders (180 bp multiples) | | Single-stranded conjugative plasmids & integrative conjugative elements |

| Protection from Nucleases | | Fully shielded inside donor-recipient cytosol & micronuclear membrane | | Shielded by vesicle lipid bilayer; degraded in recipient endolysosomes | | Exposed to extracellular DNase I / DNase1L3 & lysosomal DNase II | | Protected by single-stranded DNA-binding proteins & T4SS channel |

| Nuclear Integration Fate | | Enters nucleus during recipient mitosis; stable NHEJ/ecDNA inheritance | | Rare nuclear entry; predominantly transient cytoplasmic signaling | | Rapidly degraded in phagolysosomes; negligible heritable integration | | RecA-mediated homologous recombination or autonomous plasmid replication |

| Sensitivity to Cytoskeletal Drugs | | Abolished by F-actin depolymerization (Cytochalasin D / Latrunculin) | | Largely insensitive or enhanced by actin cortex relaxation | | Phagocytic uptake sensitive to PI3K / dynamin / actin inhibitors | | Not applicable (prokaryotic pilus polymerization) |

In the UT Southwestern experiments, thicker tunneling nanotubes containing both filamentous actin (F-actin) and microtubules acted as intracellular railways capable of accommodating intact micronuclei and chromatin bodies [1, 2] . Treating

co-cultures with low-dose actin polymerization inhibitors (such as cytochalasin D or latrunculin B) or microtubule-disrupting agents that collapse tunneling nanotube projections severely blunted the transfer of micronuclear DNA between donor and recipient cells, confirming that cytoskeletal nanotubes serve as the primary physical highway for horizontal chromosome exchange [1, 2] .

4. Nuclear Entry During Recipient Mitosis & Stable Genomic Integration

Delivering a donor micronucleus into the cytoplasm of a neighboring cell is only half the journey; to heritably alter the recipient cell's lineage, the transferred genomic DNA must cross the recipient cell's own nuclear envelope. Because an intact interphase nuclear pore complex has a diffusion channel diameter of roughly 9 nm (and a maximum active-transport dilation limit of ~39-42 nm), a megabase-scale chromatin fiber or micronucleus cannot squeeze through interphase nuclear pores [1, 4] .

Maurais, Ly, and colleagues demonstrated that transferred micronuclear DNA overcomes this topological barrier by exploiting recipient cell mitosis [1, 2] . When a recipient cell carrying a newly imported donor micronucleus enters M phase, its primary nuclear envelope undergoes phosphorylation-driven disassembly -- nuclear envelope breakdown (NEBD) -- mixing the recipient's condensing chromosomes with the cytoplasm [1] . If the donor micronuclear membrane has also ruptured or disassembled, the foreign chromatin fragment is exposed directly to the recipient's mitotic spindle apparatus.

Through protein tethers -- such as the DNA-crosslinking protein Barrier-to-Autointegration Factor (BAF) , inner nuclear membrane proteins, or DNA-damage response factors like MDC1 and TOPBP1 that coat broken chromosome ends -- the donor chromosomal fragment hitches a ride alongside the recipient's endogenous chromatids during anaphase segregation [1, 4] . When the recipient nuclear envelope reassembles around the segregated chromatin mass at telophase, the donor genomic DNA is enclosed inside the new primary nucleus [1, 2] .

Once inside the recipient primary nucleus, whole-genome sequencing of expanded recipient clones revealed two distinct mechanisms of multi-generational persistence [1] :

* Chromosomal Integration via End-Joining Repair: In many recipient clones, the transferred chromosomal fragment underwent double-strand break repair via classical non-homologous end joining (c-NHEJ) -- dependent on the Ku70/Ku80 heterodimer, DNA-PKcs, and DNA Ligase IV -- or microhomology-mediated end joining (MMEJ / Pol) , covalently ligating into an endogenous recipient chromosome as a non-reciprocal translocation or insertion [1, 4] .

* Autonomous Extrachromosomal Maintenance: In other cases, particularly when circularized acentric fragments (extrachromosomal circular DNA, or ecDNA / double minutes) or centromere-retaining minichromosomes were transferred, the donor DNA replicated once per S phase inside the recipient nucleus and persisted autonomously across dozens of cell generations without integrating into a host chromosome [1] .

5. Chromothripsis, Transcriptional Activity & Phenotypic Reprogramming

A hallmark of DNA trapped inside cytoplasmic micronuclei is its vulnerability to chromothripsis -- a catastrophic mutational process first discovered in human cancer genomes by Stephens and Campbell (2011) and mechanistically linked to micronuclei by David Pellman and Peter Ly [4] . Because micronuclear envelopes lack sufficient nuclear pore complexes to import replication factors (such as MCM helicases and RPA), DNA replication inside a micronucleus is slow, asynchronous, and incomplete [4] . When the fragile micronuclear membrane spontaneously ruptures in interphase or collapses during mitosis, cytoplasmic exonucleases (such as TREX1) and endonucleases (such as APE1) attack the under-replicated chromatin, shattering the single chromosome or chromosome arm into dozens of fragments that are subsequently stitched back together in a scrambled order and copy-number state upon nuclear re-entry [4] .

Remarkably, the 2026 Cell study shows that chromothriptic rearrangement is not confined to the cell in which the chromosome initially missegregated: shattered micronuclear chromosomes can be transferred horizontally to a neighbor and stitched together inside the recipient cell's nucleus [1, 2] . In effect, a healthy bystander cell can acquire a complex, pre-rearranged or amplified genomic cassette in a single intercellular transfer event without ever having undergone a mitotic error of its own [1] .

| Experimental Stage & Assay | | Molecular Perturbation / Input | | Observed Quantitative / Mechanistic Outcome | | Functional Impact on Recipient Cell |

| 1. Donor Micronucleation Induction | | Targeted Cas9 chromosome-arm cleavage or CENP-E / MPS1 mitotic inhibition | | Lagging chromosomes & acentric fragments encapsulated into 1-3 um cytoplasmic micronuclei | | Generates mobile cytoplasmic genomic DNA cargo |

| 2. Intercellular Transit | | Direct donor-recipient co-culture vs. Transwell separation / Cytochalasin D | | Micronuclear chromatin traffics across F-actin/tubulin tunneling nanotubes; blocked by physical separation | | Delivers Mb-scale human DNA across plasma membranes |

| 3. Nuclear Incorporation | | Recipient prometaphase nuclear envelope breakdown (NEBD) + NHEJ/MMEJ repair | | Foreign chromatin captured into telophase nucleus; integrates into host chromosomes or persists as ecDNA | | Establishes stable mitotic inheritance over >20-50 divisions |

| 4. Transcriptional Activation | | RNA-seq & fluorescent/enzymatic reporter quantification in recipient clones | | Transferred genes retain euchromatic marks, recruit RNA Polymerase II, and produce functional mRNAs & proteins | | Confers de novo enzymatic, surface-receptor, or signaling activity |

| 5. Phenotypic Selection | | Drug/antibiotic challenge (e.g., blasticidin, puromycin, or targeted therapy) | | Recipient cells lacking endogenous resistance survive and clonally expand via horizontally acquired genes | | Alters cellular survival, drug resistance, and proliferative behavior |

Crucially, the transferred genomic DNA is not transcriptionally silenced as inert heterochromatin [1, 2] . Transcriptomic and protein-expression analyses of recipient

clones demonstrated that genes encoded on the transferred chromosomal segments actively recruit host RNA Polymerase II, undergo canonical splicing and polyadenylation, and translate into functional proteins that remodel recipient cell behavior [1, 2] . In co-culture experiments, recipient cells that acquired genomic segments from donor cells gained heritable resistance to lethal pharmacological selection agents, altered their proliferation kinetics, and adopted new gene-expression signatures dictated by the horizontally acquired loci [1, 2] .

6. Evasion and Modulation of Innate Cytosolic DNA Sensing (cGAS-STING)

The discovery that megabase-scale DNA routinely transits through the cytoplasm of human cells raises an immediate immunological question: why does this transferred DNA not trigger suicidal innate immune activation? Mammalian cells are equipped with the cytosolic DNA sensor cyclic GMP-AMP synthase (cGAS) , which binds double-stranded DNA in the cytoplasm and synthesizes the second messenger 2 3 -cGAMP to activate STING (Stimulator of Interferon Genes) on the endoplasmic reticulum, driving TBK1-IRF3 phosphorylation, Type I interferon (IFN-beta) secretion, and inflammatory senescence or apoptosis [6] .

Two biophysical properties of micronuclear chromatin and tunneling nanotube transport help explain how transferred genomic DNA navigates this checkpoint [1, 4, 6] :

* Membrane and Nucleosomal Shielding During Transit: As long as the micronuclear envelope remains intact while moving along a tunneling nanotube, the chromatin is topologically compartmentalized away from cytosolic cGAS. Even when the micronuclear membrane ruptures, genomic DNA is tightly wrapped around histone octamers; structural studies show that nucleosome-bound chromatin -- and particularly chromatin coated by the high-affinity DNA-bridging protein BAF -- strongly inhibits cGAS oligomerization and catalytic cGAMP synthesis compared to naked viral or bacterial dsDNA [4, 6] .

* Chronic STING Rewiring in Genomically Unstable Tissues: In tumor microenvironments and chronically stressed tissues, sustained low-level cGAS-STING activation frequently selects for epigenetic silencing of STING or shifts downstream signaling from cytotoxic Type I interferon production toward non-canonical NF- B activation (RelB/p52), which actually promotes cytoskeletal remodeling, cellular motility, and nanotube protrusion [6] .

7. Clinical & Evolutionary Horizons: Tumor Microenvironment Evolution, Somatic Mosaicism & Gene Editing

The demonstration that human somatic cells can exchange functional chromosomal DNA carries far-reaching implications across oncology, tissue aging, and genetic medicine [1, 2] :

* Accelerated Intratumoral Heterogeneity & Drug Resistance: Over 60% to 80% of human solid tumors exhibit chromosomal instability (CIN) and abundant micronuclei [4, 6] . Previously, if a single tumor subclone amplified an oncogene (such as MYC , EGFR , or ERBB2) or a multidrug-resistance efflux pump (ABCB1 / MDR1) on an extrachromosomal or chromothriptic fragment, that trait could spread only as fast as

that single clone divided. Intercellular DNA transfer via tunneling nanotubes provides a mechanism for chromosomally unstable cancer cells to horizontally distribute amplified oncogenes or drug-resistance loci to neighboring tumor subclones -- or even to non-malignant stromal fibroblasts, endothelial cells, and tumor-associated macrophages -- rapidly reprogramming the surrounding tumor microenvironment [1, 2, 7] .

* Radiotherapy and Chemotherapy Bystander Effects: Clinical radiation therapy and genotoxic chemotherapies (such as taxanes, platinum agents, and PARP or TOP2 inhibitors) intentionally induce massive DNA double-strand breaks and micronucleation to kill dividing tumor cells [1, 4] . The finding that micronucleation triggers horizontal DNA export suggests that sub-lethally irradiated cells may shed damaged or rearranged chromosomal fragments into surviving neighbors before dying, potentially seeding secondary genomic rearrangements in adjacent tissue [1, 2] .

* CRISPR-Cas9 Genome Editing Safety: Targeted CRISPR-Cas9 endonucleases generate site-specific double-strand breaks that can occasionally produce acentric chromosome arm fragments and micronuclei in a small fraction of edited cells [1, 4] . Understanding how Cas9-induced micronuclei can transfer between contacting cells provides a new quantitative framework for evaluating off-target chromosomal mosaicism in ex vivo and in vivo therapeutic gene-editing protocols [1] .

By proving that the nuclear genome of human somatic cells is not an inescapable island, the UT Southwestern discovery bridges classical eukaryotic cell biology with the dynamic network genetics long associated with the microbial world -- revealing a hidden physical layer of genetic communication operating across human tissues [1, 2] .

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