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Report

A Virus Causes Cancer by Inducing Massive Chromosomal Instability through Cell Fusion

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Summary

Chromosomal instability (CIN) underlies malignant properties of many solid cancers and their ability to escape therapy, and it might itself cause cancer [1, 2]. CIN is sustained by deficiencies in proteins, such as the tumor suppressor p53 [3–5], that police genome integrity, but the primary cause of CIN in sporadic cancers remains uncertain [6, 7]. The primary suspects are mutations that deregulate telomere maintenance, or mitosis, yet such mutations have not been identified in the majority of sporadic cancers [6]. Alternatively, CIN could be caused by a transient event that destabilizes the genome without permanently affecting mechanisms of mitosis or proliferation [5, 8]. Here, we show that an otherwise harmless virus rapidly causes massive chromosomal instability by fusing cells whose cell cycle is deregulated by oncogenes. This synergy between fusion and oncogenes "randomizes" normal diploid human fibroblasts so extensively that each analyzed cell has a unique karyotype, and some produce aggressive, highly aneuploid, heterogeneous, and transplantable epithelial cancers in mice. Because many viruses are fusogenic, this study suggests that viruses, including those that have not been linked to carcinogenesis, can cause chromosomal instability and, consequently, cancer by fusing cells.

Results

To test the hypothesis that viruses can induce chromosomal instability (CIN) by fusing cells, we compared three aliquots from the same population of normal diploid human D551 fibroblasts that we modified in three ways. We derived one population (Figure 1A.1, "D") by cotransducing an aliquot of D551 cells with two oncogenes, adenoviral *E1A*, which deregulates the cell cycle by inactivating the tumor suppressor *RB1*, and human *HRAS1*, which prevents *E1A* from triggering apoptosis. Human cells cotransduced only with *E1A* and *HRAS1* do not form tumors in animal models of carcinogenesis [9].

We derived the second population (Figure 1A.2, "DV") by first infecting another aliquot of D551 cells with $MPMV^E$, a primate retrovirus that has been found in people and has no cytostatic or cytotoxic effect [10]. The infected cells remained diploid and mononuclear because normal cells that are fused by the addition of $MPMV^E$ cease proliferation and die within a few weeks, whereas cells that become infected do not fuse to each other, which prevents the emergence of new fused cells [10]. Therefore, we waited for about a month until the fused cells died, and then we cotransduced *E1A* and *HRAS*. Thus, the resulting DV cells expressed the oncogenes and were infected with the virus but were never fused.

The third population also expressed both oncogenes and was infected with the virus, but the cells were hybrids (Figure 1A.3, "DVH1," "DVH2," and "DVH3") that we created by transducing the third aliquot of D551 cells with either *E1A* or *HRAS1* and then fusing the resulting cells to each other by $MPMV^E$.

A Synergy of Cell Fusion and Oncogenes Induces Massive CIN

Within the few generations required for obtaining enough cells for analysis, we found that the hybrid populations (DVH1–DVH3) were highly heterogeneous in their DNA content, as detected by flow cytometry, whereas the control cells (D and DV) were not (Figure S1 in the Supplemental Data available online). Because DVH and DV both expressed the oncogenes and the virus but only DVH cells were formed by fusion, we concluded that the heterogeneity was a consequence of cell fusion. The diversity of the hybrids decreased noticeably while the populations were expanding, perhaps as a result of selective pressure of tissue culture (Figure S1, compare left and right histograms). Consistent with the reports that CIN causes apoptosis [11], the rate of apoptosis in the hybrids was higher during the expansion than in D or DV cells (Figure S1). As expected, expression of *E1A* with *HRAS* increased the rate of proliferation (Figure S1, right column).

Karyotype analysis of the expanded populations revealed that the chromosomal heterogeneity was substantially higher in the hybrids than in the control cells. Karyotypes of control cells (D and DV) were relatively stable, uniform, and usually hypodiploid with relatively few chromosomal abnormalities (Figures 1B and 1C). In contrast, the karyotypes of the hybrids were highly aneuploid, from hypodiploid to octaploid (Figures 1B and 1E), and were heterogeneous with respect to both the number of chromosomes and the number of

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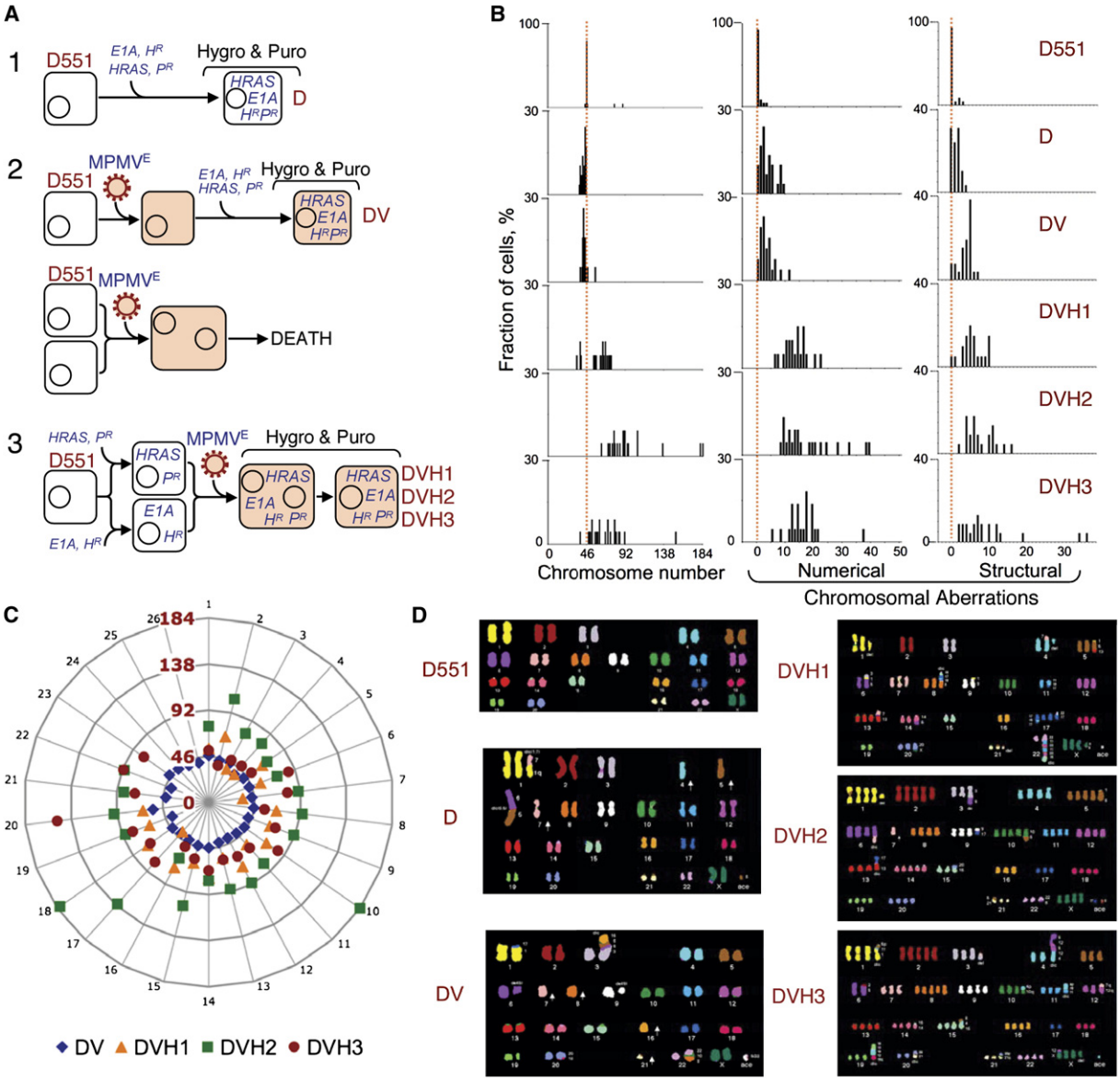

Figure 1. A Synergy between Virus-Mediated Cell Fusion and Oncogenes Induces Genomic Heterogeneity

(A) Experimental design. Detroit 551 normal human fibroblasts (D551 cells) were cotransduced with *E1A* in a vector that also confers resistance to hygromycin (H^R) and with *Ha-RasV12* (*H-RAS*) in a vector that confers resistance to puromycin (P^R) (1). To control for the effects unrelated to cell fusion, we produced cells that were infected with $MPMV^E$ and cotransduced with *E1A* and *H-RAS* but were not fused (2; see text for details). Alternatively (3), we transduced D551 cells with either E1A or H-Ras by using the same vectors as in (1) and (2) and then fused them to each other with $MPMV^E$ (Supplemental Experimental Procedures). Three colonies of cells resistant to both selection drugs (DVH1, DVH2, and DVH3) were chosen randomly from one plate. (B) A synergy of virus-mediated cell fusion and oncogenes induces massive chromosomal instability. The indicated cell populations of 10^8 each were obtained as described in Figure 1A and Figure S1 and were analyzed via karyotyping for chromosome number (left column), numerical aberrations (middle column), and structural abnormalities (right column). The number of cells used for each cell line was between 19 and 24. Note that the data for D551 are plotted on a different scale than the data for other cells. The heterogeneity of the chromosome number in the analyzed cells is presented in (C). The concentric circles indicate the chromosome number per cell, each symbol corresponds to one cell, and the spokes correspond to the cell's identifying number. Note the contrast between the uniformity of DV cells and the diversity of the hybrids. (D) A SKY image from one representative cell from each population is presented. The white arrows refer to chromosome losses. See Table S1 for the karyotype annotations.

numerical and structural aberrations, which included chromosome breakage and endoreduplication (Figures 1B–1E; also Figure S2).

The differences detected by spectral karyotyping (SKY), which reveals aberrations undetectable by conventional karyotyping [12], were even more remarkable (Figure 1D). Whereas the cotransduced cells had few structural abnormalities or deviations in chromosome number, all the hybrids were diverse to the degree that each out of about ninety analyzed cells had a unique karyotype. A distinguishing feature of the hybrids was complex rearrangements involving multiple chromosomes (Figure 1D; also Tables S1 and S2 and Figure S2). The clonal chromosomal imbalances in the hybrids were

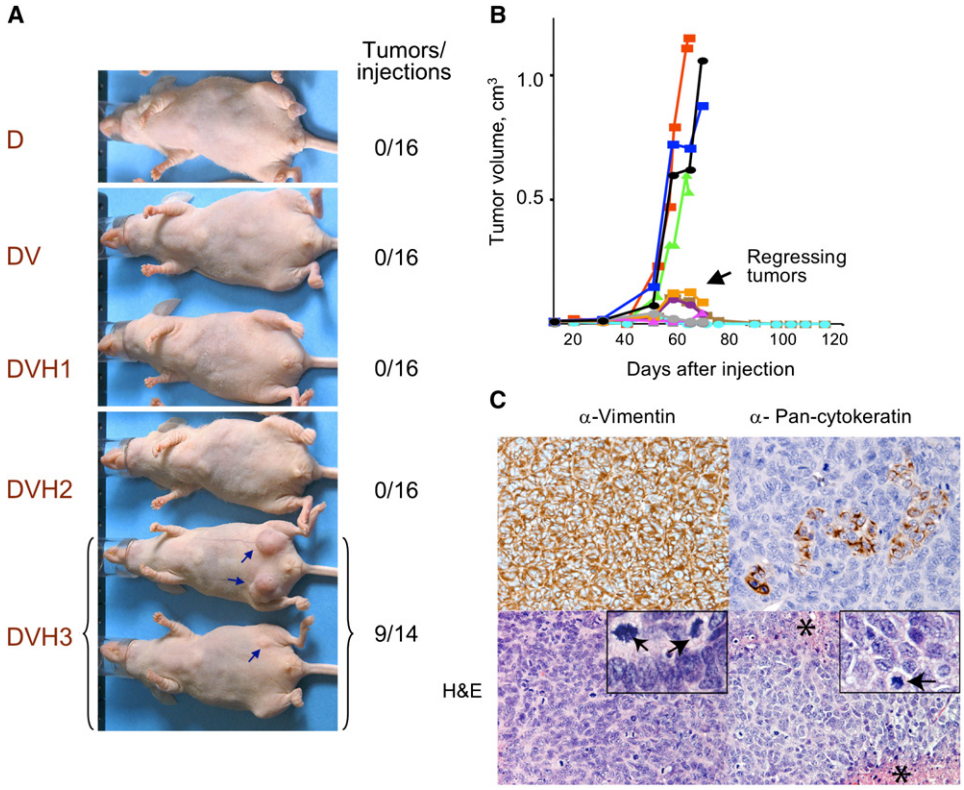

Figure 2. A Synergy of Cell Fusion and Oncogenes Produces Cancers

Cells (5×10^6) of the indicated populations that were expanded to 10^8 cells (Figure S1) were injected subcutaneously into both flanks of 6- to 8-week-old irradiated nude female mice, and the mice were monitored for the appearance of tumors, indicated by blue arrows in (A). The growth of tumors is plotted in (B). Each line in (B) is a history of one injection that gave rise to a tumor, and the total tumor frequency is indicated in (A). The picture in (A) was taken 6 weeks after injection. Two tumors produced by injection of DVH3 cells (DVH3-t1 and DVH3-t2) were analyzed by histology and immunohistochemistry. An example is shown in (C). Asterisks show necrotic regions; arrows (insets) show mitotic figures. One of the mice injected with DV developed a primary (of mouse origin) anal skin cancer that was away from the injection site and was detected at day 120 after injection. All mice were monitored for more than 10 months after injection until their death, or until the tumor burden was the maximal allowed for the animal's welfare.

reminiscent of karyotypes of cancer cells [13]. Because all this genomic diversity was derived from just a few cells and changed over time (Figure S1, compare left and right histograms) we concluded that $MPMV^E$ induced massive chromosomal instability by fusing cells "primed" with the oncogenes. The degree of CIN and the diversity of chromosomal aberrations by far exceeded those reported in cells that became aneuploid after drug-induced failure of cytokinesis [4].

The number of chromosomal aberrations in the hybrids was not simply a result of the hybrids' having more chromosomes than the control cells. In fact, the number of numerical aberrations per chromosome was *inversely* proportional to the number of chromosomes per cell (Figure S3, left column), which could be explained if cell fusion induces chromosomal instability by means other than merely duplicating the genome.

A Synergy of Cell Fusion and Oncogenes Is Tumorigenic

To test whether chromosomal instability promoted tumorigenicity, as the evolutionary model of cancer hypothesizes [14], we transplanted the hybrid and control cells into nude mice (Figure 2). As expected [9], cotransduced cells (Figures 2A and 2D) failed to induce tumors, as did cotransduced cells infected with the virus (Figure 2A, "DV"). In contrast, one of three hybrid populations produced tumors (Figure 2A, "DVH3," and Figure 2B).

Surprisingly, histopathologic examination revealed that these fibroblast-derived tumors did not exhibit the typical fusiform cell shape and fascicular cellular arrangement characteristic of fibroblast-derived malignant tumors (fibrosarcomas). Rather, the tumors comprised more primitive looking cells that had epithelial-like morphology and were arranged in nests and cords. Virtually all of the cells expressed vimentin, an intermediate filament associated with mesenchymal differentiation but also with aggressive epithelial-derived tumors (carcinomas). An aggressive phenotype was also indicated by alternating regions of highly proliferative and necrotic tumor cells (Figure 2C).

The remarkable observation that fibroblasts produced tumors with aberrant—focally carcinomatous—differentiation could be explained if chromosomal instability were sufficiently extensive to generate cells with diverse phenotypes. An alternative explanation is that the tumors represented an accidental contamination with an unrelated epithelial cancer cell line. However, the microsatellite analysis estimated the chance

of a contamination at less than one in 10^9 (Figure S4). Thus, the morphological and immunohistological features of the tumors raised the possibility that at least some epithelial tumors might not be of epithelial origin and illustrated the randomizing power of cell fusion. The ability of cell fusion to change epigenetic regulation of cells [8] or expression of oncogenes could also contribute to the change in morphology.

DVH3 cells could also become carcinogenic as a result of mutations acquired before cell fusion. For several reasons, we found this possibility unlikely. Oncogenic mutations were unlikely to have occurred in D551 cells because we made all cell lines simultaneously from the same D551 population (Figure 1A), but only DVH3 cells became carcinogenic. Transduction of *E1A* and *HRAS* could promote mutagenesis, but consistent with the previous report [9], culturing the control cells (D and DV) for at least a month failed to make them tumorigenic (Figure 2), which made it unlikely that culturing the parental cells of the hybrids that were made only 4 days before fusion (Supplemental Experimental Procedures) would result in oncogenic mutations. Finally, tumors formed in mice by human fibroblasts cotransduced with *E1A* and *HRAS*, along with other oncogenes, such as *MYC* [15] or *hTERT* [9], were fibrosarcomas, whereas tumors formed by DVH3 were not (Figure 2C).

Carcinogenic Hybrids Evolve

Several observations suggested that, as envisioned by the evolutionary model of carcinogenesis [14], the tumor cells were a minute fraction of the parental cells and were produced by CIN and then selected in the animal for their ability to form tumors. One such observation was that of a shift from the karyotypic diversity caused by CIN in the parental cells (Figure 3A and 3C, "DVH3") to a relatively uniform chromosome number in tumor cells (Figure 3A and 3C, "DVH3-t1" and "DVH3-t2"). Additionally, there were recurrent and clonal numerical and structural chromosome aberrations detected in both analyzed tumors but not in parental cells by conventional karyotyping (Figure 3A) or SKY (Figure 3B). A third observation was that the tumors that developed in the same animal as a result of injecting two identical aliquots of cells had distinct genomes even though they shared marker chromosomes (Figure 3B; compare DVH3-t1 and DVH3-t2). Finally, the outcome of the injections was not predetermined because some tumors grew aggressively, others regressed, and some did not form at all.

The finding that the tumors were formed by a minor subpopulation of DVH3 cells further supported our conclusion that the tumorigenic subpopulation emerged during the clone progression rather than before the hybrid was created.

The increased tumorigenicity of the explanted cells (Figure 4) provided functional evidence for Darwinian selection of tumorigenic cells in the animal. The explanted cells always produced tumors if they were injected into animals (Figure 4A), and these tumors grew twice as rapidly as those induced by DVH3 cells (compare Figures 4A and 2B) and were more aggressive, as indicated by their acquired ability to invade through the peritoneal wall (Figure 4C) and disseminate to visceral organs (Figures 4C–4F). In addition, these tumors included areas of clear cell differentiation (Figure 4B), and these areas were not observed in the original tumors, indicating an evolution of the histological properties. Thus, we concluded that a synergy between cell fusion and oncogenes produced CIN that persisted in the progeny, resulted in cells capable of forming tumors, and was likely to fuel their progression to a more aggressive phenotype.

Discussion

Our findings provide a simple model that explains how CIN can occur in sporadic cancers without mutations that directly affect chromosome segregation. Several observations suggest that this mechanism can function in vivo. Indeed, the key step of the proposed mechanism, fusion of cells by viruses, is known to occur in the body [16]. Cell fusion has been detected in human cancers and might be explained by the activity of viruses, exogenous or endogenous [17–19]. Remarkably, the karyotypes produced by fusion in our system are indistinguishable from karyotypes of human cancers [13], which implies that determining whether an aneuploid cancer cell is *not* a hybrid may be difficult. Finally, although the fate of cells fused by viruses in the body is not known, even though fusogenic viruses have been explored as therapeutic tools [20], there is no reason to assume that fusion would cause CIN in the dish but not in the body. Considering that the frequency of cancers relative to the number of cells in human populations is astronomically small, the carcinogenic outcome of the mechanism that we described may not need to be as frequent as that found in our study to contribute to carcinogenesis. However, testing whether this mechanism indeed functions in vivo would require animal models and approaches to detecting proliferating hybrids in the body.

We estimate that at least 18 of 29 virus families that infect human cells have species that fuse cells, which implies that CIN and, by implication, cancer might be caused by many viruses, including those that are considered commensal. Pre-existing mutations that affect the cell cycle may not be required for CIN even if only one of the fusion partners is a stem cell; stem cells are frequently recruited to sites of infection because their plastic cell-cycle regulation allows proliferation after fusion [21]. Furthermore, viruses that carry oncogenes and are fusogenic would provide both components required for induction of CIN literally in one package. Viruses might also collaborate. For example, one can speculate that, whereas human papillomavirus (HPV) deregulates the cell cycle with oncoproteins E6 and E7 [22], herpes viruses or other fusogenic viruses associated with HPV infection can fuse the cells and thus cause CIN. Importantly, in principle the fusogenic virus does not need to be in the fused cells, which implies that the model that we propose could be an example of a "hit-and-run" type of viral carcinogenesis [10].

Why cell fusion induces chromosomal instability that is maintained throughout the generations of the cells is not known. One possibility is that cell fusion has the same effect as the drugs that inhibit cytokinesis [4], specifically, that it causes tetraploidy and the ensuing spontaneous chromosomal loss. However, we find that the

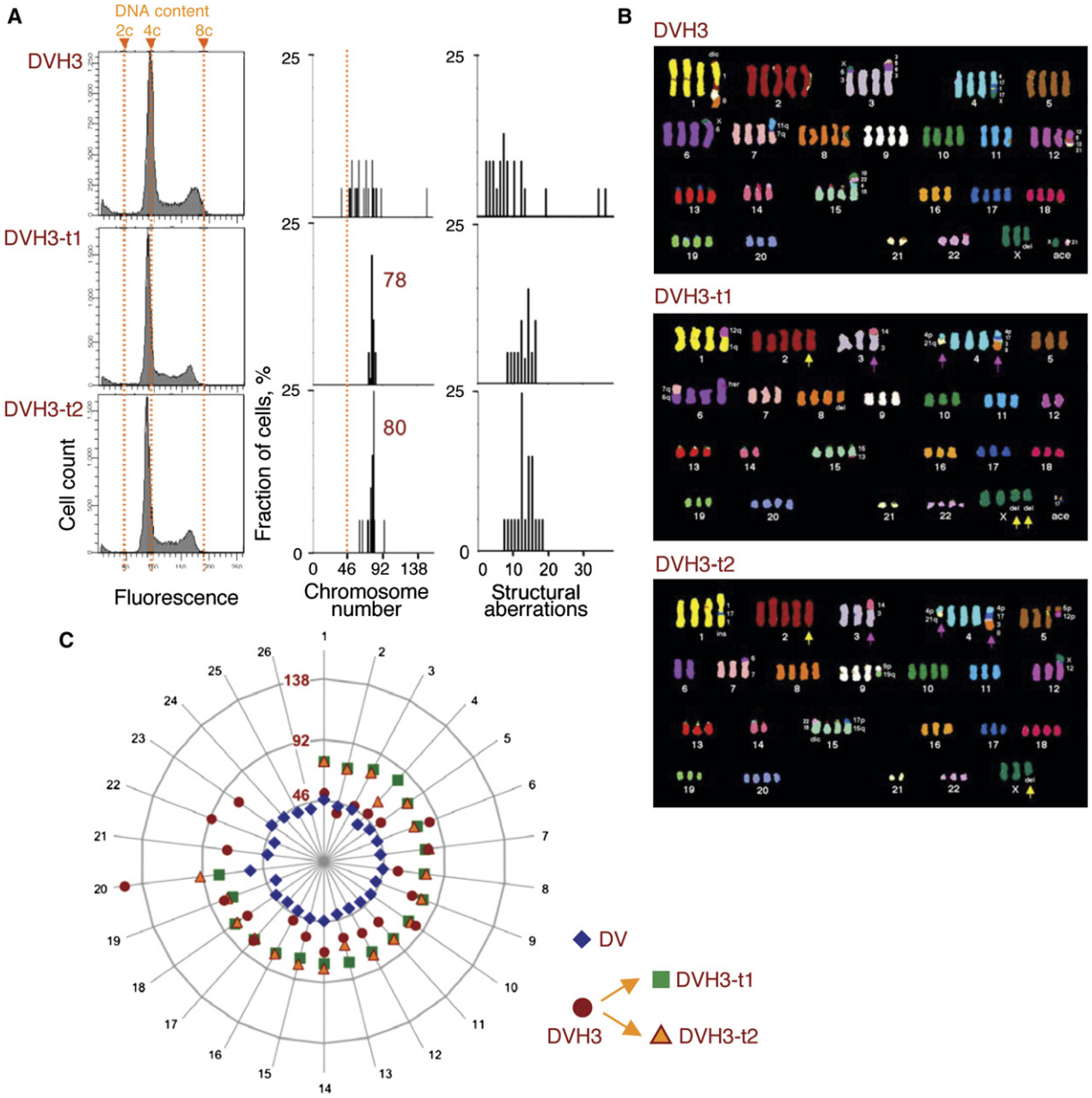

Figure 3. Cancer Cells Are Selected in the Animal from a Diverse Population Generated by CIN

Cells explanted from tumors (DVH3-t1 and DVH3-t2) were analyzed for DNA content by flow cytometry ([A], left column), and for chromosome number and structural aberrations by conventional banding with DAPI ([A], middle and right columns, respectively) and by spectral karyotyping (B). If it could be identified, the modal number of chromosomes is noted in the middle column in (A). For DVH3-t1 and DVH3-t2, 20 spreads were analyzed for each. The yellow arrows indicate a numerical (+2) and a structural [del(X)] aberration that are clonal and recurrent in the tumor cells. The magenta arrows indicate clonal aberrations found in the tumor cells. The heterogeneity of the chromosome number in the analyzed cells is presented in (C). The concentric circles indicate the chromosome numbers, and each symbol corresponds to one cell. The cells are numbered by the spokes.

number of chromosomal abnormalities caused by fusion by far exceeds that reported for cells that fail cytokinesis [4] and does not require propagation in mice. This difference can be explained by the fact that cell fusion does not merely mimic failed cytokinesis or endoreduplication, which simply duplicate the genome. Instead, the destabilizing effect of cell fusion could be a result of differences between the parental cells [23]; such differences could include acquired mutations, telomere length, the stage of DNA replication, epigenetic regulation, and other properties.

For example, the difference in the cell-cycle position of parental cells often results in premature chromosome condensation (PCC), which has been observed in cancer [8]. The chromosome fragments produced by PCC are randomly incorporated into chromosomes of daughter cells [24], which might explain the massive chromosomal aberrations of the hybrids. The hybrids may also retain properties of the parental cells, which can further expand their diversity and account for emerging properties, such as the ability to metastasize [23] or become drug resistant [25]. The experimental model that we

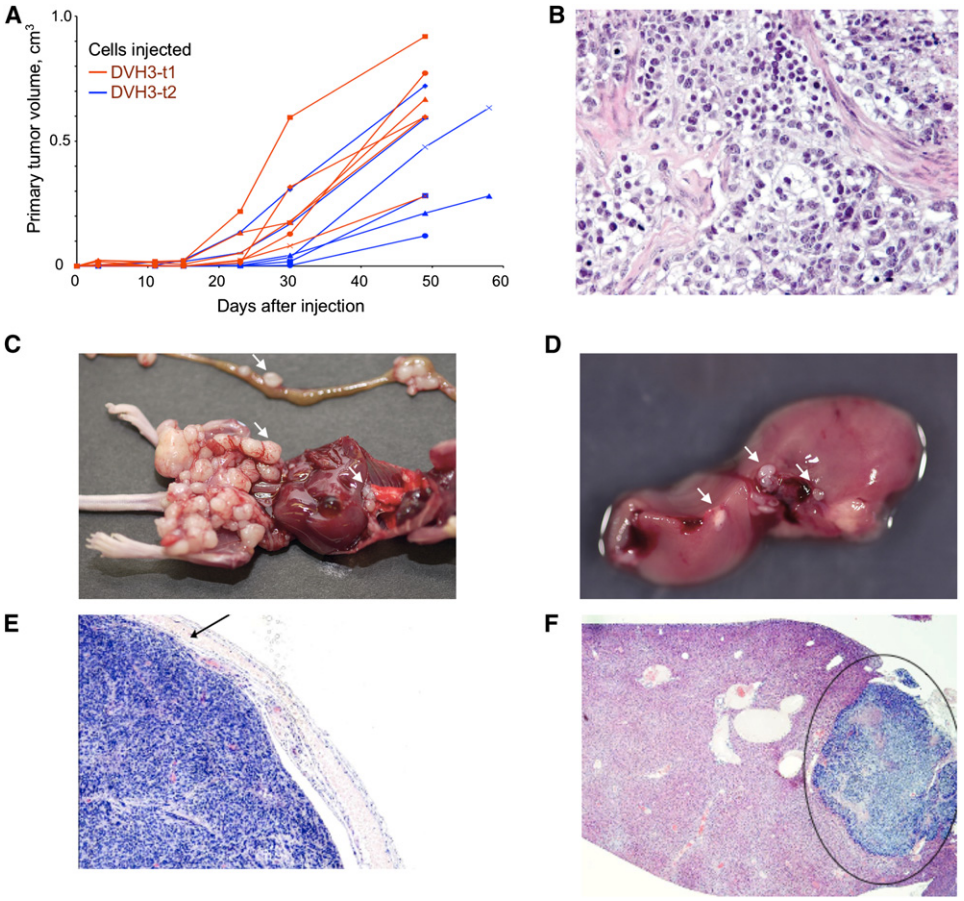

Figure 4. Tumors Produced by the Hybrids Are Transplantable Invasive Carcinomas

The explanted tumor cells (DVH3-t1 and DVH3-t2, Figure 3) were expanded to 4×10^7 cells and injected at 5×10^6 into the flanks of nude mice with six injections for each explant, and the growth of the tumors was monitored (A). Each line in (A) represents a history of one injection. The history of all injections is plotted. Upon histologic analysis, some of the tumors showed marked regional heterogeneity, including the areas of clear cell differentiation shown here. (B). A preparation of one of the mice injected with DVH3-t1 (C) illustrates the spread of the cancer into the peritoneum and some visceral organs, including the intestine (C and E) and the liver (D and F). (E) A small segment of intestinal mesentery (arrow) is superficially attached to (and dwarfed by) a large tumor nodule. (F) A tumor nodule (circled) invades the outside of the liver. The pattern of the tumor spread was similar in all six injected mice, except that the spread was more extensive and the size of the tumor nodules was larger in DVH3-t1 than in DVH3-t2.

developed may help to shed light on the mechanisms of genomic and, perhaps, epigenetic instability and may help with studying the consequences of these conditions.

The mechanism of carcinogenesis and tumor progression that we propose is consistent with the reality that the diversity of cancer cells and their ability to evolve together make available therapies largely ineffective and suggest that early detection or prevention are likely to remain the most successful ways of conquering this disease. For example, immunizations against HPV are strikingly effective in preventing cervical cancer, and immunization against hepatitis B virus (HBV) substantially decreases the incidence of liver cancer. Our study suggests that many viruses can contribute to carcinogenesis in a previously unrecognized way. Therefore, if our model is correct, protecting the body against these viruses or preventing the cell fusion that they cause may decrease the frequency of cancers and prevent their progression.

Supplemental Data

Supplemental Experimental Procedures, four figures and three tables are available with this article online at http://www.current-biology.com/cgi/content/full/17/5/431/DC1/.

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