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Science 330, 46 (2010);
DOI: 10.1126/science.1195991

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Mosaicism—Switch or Spectrum?

Brian R. Davis and Fabio Candotti

Somatic revertant mosaicism—the coexistence of cells carrying inherited genetic mutations with cells that have undergone spontaneous changes that correct the mutant phenotype—was previously thought to be extremely rare in terms of the frequency with which patients exhibit revertant mutations. A number of recent findings, including the report by Choate et al. on page 97 of this issue (1), challenge this perspective.

Somatic revertant mosaicism has been described in several genetic disorders affecting self-regenerating organ systems such as the skin, blood, and liver (2). Its development involves at least three steps: the occurrence of a correcting mutation in the already mutated gene; the survival of cells that have acquired partial or full functional restoration of the gene (revertant cells); and the selection and enrichment of these cells (see the figure). At present, little is known about the specific molecular mechanisms leading to revertant mutations (either during normal DNA replication or in response to genotoxic agents) or the precise selection processes for revertant cells. This limited knowledge derives from isolated reports of revertant patients carrying only one or a small number of revertant genotypes (2). As such, the commonly accepted picture has been that reversion is a highly inefficient stochastic process, possibly associated with unique characteristics of the patient exhibiting reversion.

Reports of multiple, independently arising, correcting, or second-site revertant mutations in the same patient have changed this notion and indicate that reversion is less unusual than had been thought. For example, revertant patches of healthy skin surrounded by the easily blistered skin in the disease junctional epidermolysis bullosa can arise from different molecular reversion events in the mutated genes (COL17A1 or LAMB3) in the same patient (3, 4). This was not an infrequent occurrence; multiple revertant patches, each caused by a different molecular event, were identified in up to 30% of patients (5). Recent reports from primary immunodeficiency syndromes, such as the Wiskott-Aldrich syndrome (in which reversion occurs in 10 to 15% of patients) and severe combined immunodeficiency (caused by mutations in CD3 zeta or RAG1 genes), have also documented multiple independent reversion events in patients (6–12). For example, at least 35 distinct revertant mutations were identified in one Wiskott-Aldrich syndrome patient (6, 7).

Taken together, these findings suggest that mosaicism develops through the ongoing generation of somatic mutations that affect the disease-causing gene in cells of self-regenerating organ systems. Although most of these somatic mutations will provide no benefit, some will result in partial or full functional restoration of the gene. Model calculations—taking into account the spontaneous DNA mutation rate and the number of cell divisions occurring in the newborn thymus—predict that cells that have corrections for specific immune gene mutations (e.g., correction of a stop codon) likely originate in most (or all) patients. A possible principal factor that distinguishes those individuals in which such events result in detectable revertant mosaicism is whether beneficial reversion mutations originated in a cell sufficiently early in its developmental pathway to provide for substantial expansion of revertant cells (such as epidermal stem cells for epidermolysis bullosa, and hematopoietic stem cells for lymphoid and thymic precursor cells for Wiskott-Aldrich syndrome), or perhaps otherwise in a particularly long-lived cell that is capable of expansion.
(such as a T lymphocyte for Wiskott-Aldrich syndrome). In this context, somatic revertant mosaicism is less likely a binary switch in which a given patient is either revertant or not. Rather, it appears to be a spectrum in which a patient originated revertant cells at some time, with the frequency, diversity, and functionality of the revertant cells dependent on various factors including the strength of selection. It is very possible that ultradense sequencing methods that can detect rare gene variants can test the accuracy of this picture.

In their investigations on the skin disease ichthyosis with confetti (IWC, also known as congenital reticular ichthyosiform erythroderma), Choate et al. show that independent revertant clones, originating by loss of a heterozygous mutation on chromosome 17q, give rise to the thousands of normal skin spots that appear early in life in affected patients and increase in number and size over time. By mapping the location of common genetic recombination events in the revertant clones, the authors determined that dominant frameshift mutations in the KRT10 gene cause the disease and discovered an unprecedented diversity of independent recombination events in humans. A common feature of the various KRT10 mutations is the expression of a mutant keratin protein that mislocalizes to the nucleus. Although another skin disease, epidermolytic ichthyosis, is caused by dominant negative or recessive mutations in the same KRT10 gene, revertant clones have not been identified in this condition. As such, Choate et al. postulate a link between IWC mutant keratin 10 proteins and the high number of observed mitotic recombination events. If this is correct, increased mitotic recombination should affect chromosomes other than chromosome 17q. However, it may not be necessary to invoke a specific facilitating role of the mutant keratin 10 proteins in determining the occurrence of revertant skin patches in IWC. Indeed, the function of keratin 10 may be more severely affected by the IWC frameshift mutations than by the missense substitutions responsible for epidermolytic ichthyosis.

If that is the case, revertant cells may be conferred a stronger selective advantage in IWC than in epidermolytic ichthyosis, thus allowing them to rise above the detection threshold by forming the “confetti” spots.

Somatic revertant mosaicism can be likened to a natural form of gene therapy, and the findings of Choate et al. have potential relevance to therapeutic options for affected patients. These include using revertant stem cells (from patches of corrected skin) for engraftment; expanding preexisting corrected cells in vivo; and guiding efforts to induce targeted (site-specific) revertant mutations in vivo. For the latter, studies of revertant patients are particularly important, as they could inform the levels of correction that need to be achieved by gene therapy to obtain meaningful clinical effects.

References

10.1126/science.1195991

ASTRONOMY

A Dance of Extrasolar Planets

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aunched in March 2009, the Kepler mission is tasked with searching for extrasolar planets. It continuously monitors 156,000 stars in a ~100-square-degree patch of sky covering a portion of the galactic disk centered on a direction lying in the constellation Cygnus (1). On page 47 of this issue, Holman et al. (2) report the discovery of a transiting planet whose orbit of 38.9 days varies by up to 1 hour due to the interaction with other planets in the system. This Saturn-sized world, known as Kepler-9c, circles a Sun-like star 2300 light-years away in the direction of the constellation Lyra, and is part of a bizarre system containing three transiting planets, whose mutual gravitational tugs generate an exquisitely choreographed orbital dance. Far from being mere curiosities, the planets of the Kepler-9 system may provide vital clues to the mechanisms of planetary formation and orbital evolution.

Kepler can detect a 1/10,000 dip in brightness that occurs when an Earth-sized planet on an Earth-like orbit makes a ~12-hour passage (transit) in front of a Sun-sized star. The goal is to continuously monitor its target stars for a long enough period (at least 3.5 years) to observe repeated passages by Earth-sized planets on Earth-like orbits, leading to an estimate of the occurrence frequency of potentially habitable worlds.

Although Earth-sized planets have not yet been reported, Kepler has been remarkably productive in finding hot short-period planets with orbits ranging from days to weeks. In January of this year, its first five discoveries of four “hot Jupiters” and a “hot Neptune” were announced (3), and in June, an additional 312 candidate planets were reported (4). Although the members of this latest batch of planets require follow-up observations for individual confirmation, their bulk statistics suggest that an important, and perhaps even the dominant mode of planet formation in our galaxy looks nothing like what happened in the Solar System: “Super-Earths” with masses between 5 and 15 times that of Earth are commonly found on orbits with periods of 50 days or less, with recent indications that up to a half of nearby Sun-like stars harbor objects of this type (5).

Kepler’s discoveries are contributing to a rapidly growing catalog of transiting extrasolar planets, yielding planetary masses, radii, bulk compositions, atmospheric constituents, and even weather reports (6). Furthermore, transiting planets in favorably constructed multiple-planet systems will exhibit measurable variations from strict orbital periodicity that can operate as detailed probes of the orbital dynamics (7, 8).

Although extrasolar transit-timing variations have proved elusive until now, astronomers have had centuries of experience with the transit-timing technique in our own Solar System, engaged in searching for Earth-like planets in our own solar system.