Inheritance of Somatic Mutations: Proposal of a Mechanism

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ABSTRACT: The double minute chromosomes that proliferate in response to external stimuli may be a means of genetic exchange between cells that would affect the rate and direction of evolution.

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Evolution by natural selection occurs by disproportionate disappearance from a population of lineages expressing a less adaptive gene. For selection to occur, heritable alternatives must exist. In a metazoan, the mutation providing a new alternative is presumed to be a random event that occurs, and only rarely, in a reproductive cell or its progenitor. Such a mutation is even less commonly beneficial. If heritable variations arising de novo in somatic cells multiplied in response to extrinsic factors and traveled to the reproductive cells, evolution, the rate of which is debated (Haldane, 1957; Kimura, 1968; Maynard Smith, 1968), could proceed more rapidly and in a directed manner.

Cultured cells subject to toxic agents, such as the chemotherapeutic agent methotrexate (MTX) (Schimke et al., 1978), and pathological cells in vivo (Bertino et al., 1963; Marinello et al., 1980) carry extrachromosomal fragments of DNA that are called double minute chromosomes (DMCs). In the presence of MTX, cells in culture produce by gene amplification DMCs that carry genes for dihydrofolate reductase (DHFR) in sufficient number to counter the suppression by MTX of the DHFR, the mRNA transcription for the enzyme being unaffected by the drug (Alt et al., 1976). Cellular resistance to MTX is proportional to the number of gene copies for DHFR in cell lines with either stable or transient resistance (Schimke et al., 1977). Cells with stable resistance have incorporated the extra DHFR genes into the genome. Cell lines from the ovaries of the Chinese hamster carry the amplified gene in one region of a single chromosome (Nunberg et al., 1978), perhaps at the site of the pre-existing gene. Subject to constant concentration of MTX, the transiently resistant cells carry a steady state complement of unincorporated genes for DHFR that presumably reflects a balance between the rates of production and loss of DMCs. When grown in the absence of MTX, transiently resistant cells loose their unincorporated DMCs and resistance to MTX (Alt et al., 1978). Alt and associates feel that during cell division in cultures without MTX differential apportionment or dismemberment of the DMCs leaves some daughter cells with an insufficient complement of the DHFR gene to overcome subsequent challenge with MTX, thereby causing their death. Another possible means of loss of DMCs is shedding by the cells.

I hypothesize that the shedding of DMCs may be a means for conjugation between adjacent or remote cells in a metazoan, analogous to that between unicellular organisms (Lederberg and Tatum, 1946). Cells within an organism are identical by descent except for the mutations that follow the separation of the cells by division. To share the benefit, one somatic cell might duplicate a beneficial mutation as a DMC and shed it, either in naked form or coated against enzymatic attack. Or, if encoded by a RNA viral vector, the genetic information on the DMC could travel to the reproductive cells as Temin (1976) and Steele (1979) have proposed. Surviving travel through the extracellular space or vascular system, the genetic information then could be incorporated by another cell, as is a transforming virus or as can be induced in vitro (Ruddle, 1980). This hypothesis contradicts Weismann (in Morgan, 1926), but not Darwin and Wallace (1858).

Novel genes may arise haphazardly or under epigenetic direction; my hypothesis takes no account of their origin. Rather it focuses on the production of genetic messengers that travel between cells. With such messengers, organisms could evolve more rapidly because all of the somatic cells could provide alternatives for selection. The resulting evolutionary change would occur, in one sense, under environmental direction. For reasons of natural selection, cells normally should produce extra copies only

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of beneficial genes. This discriminating production of genes would be a form of pre-selection that would not depend on differential mortality or reproduction.

Incorporation of adaptive genes by somatic or reproductive cells would benefit the organism. An extrinsic cue to the extra-ordinary production of a gene unique to one cell probably would act on neighboring cells as well, or on the entire organism. Other cells would benefit immediately from the spread of a beneficial gene. With the spread of the beneficial trait, the organism would be more likely to survive to reproduce. Export of a novel gene to reproductive cells or their progenitors would allow passage of a trait between generations, thereby increasing the fitness of future generations.

In some cases, deleterious traits arising in the soma pass between generations, as can induced diabetes (Goldner and Spergel, 1972) or hypothalamic anomolies (Bakke et al., 1975). Selection should act against organisms expressing deleterious genes. However, a gene, e.g. of viral origin (Temin, 1974), that can force its own replication can benefit even if the organism as a whole does not (Dawkins, 1976). The spread of such genetic material might be a source of inherited disease, as are transforming viruses, or a cause of the metastatic proliferation of tumors. DMCs, as well as agents such as proviruses (Temin, 1976; Steele, 1979), are possible agents of such commerce in genes between cells.

The inheritance of somatic mutations is most likely a genetical response to chronically active stimuli. While extrachromosomal fragments may appear quickly, the rate of incorporation by other cells should be slow for reasons of genetic economy. Failure by the immigrant gene to incorporate into the genome of the recipient might account, in fact, for the decreasing transmission to succeeding generations found by Gorczynski and Steele (1981). Chronic irritants are more likely to outlast the individual or to reoccur in later generations, making evolutionary rather than physiological response telelogically sensible. The production of extrachromosomal fragments of DNA make it possible.

In the theory of Pangenesis, Darwin (1896) postulated gemmules of heritable information travelling between somatic and reproductive tissues. However, since Galton's (1871) and Weismann's (in Morgan, 1926) apparent refutations by experiment and Sutton's (1903) hypothesis on the chromosomal basis of inheritance, the generally accepted theory on evolution has focused implicitly on the genes in reproductive cells. Epigenetic theories, alternatives constructed to rationalize the rate and complexity of evolution, focus on the inheritance of acquired characteristics (Waddington, 1957). Such theories propose that the adaptability of an organism translates into adaptations by directed mutations. However, the mechanism of this direction has yet to be stated as a testable hypothesis. Genetic exchange between somatic and reproductive cells could speed and direct evolution without directing mutation itself.

The exchange of genetic information between cells may occur generally. Or, other than by proviruses, it may be limited to instances such as resistance to methotrexate. Not withstanding this possible limitation, the hypothesis on genetic exchange between cells can be tested with MTX-resistant cells. An auxotrophic mutant with double minute chromosomes bearing the supernumerary genes for DHFR could be grown together with phototrophic cells without double minute chromosomes or resistance to methotrexate. Following growth on complete and then deficient media, the surviving cells could be examined for DMCs bearing DHFR genes by fluorescence (Kaufman, et al., 1978) or by challenge with methotrexate.

Experimental evidence on the passage between generations of characters arising in the soma challenges the generally accepted Weismann Doctrine. The rise in abundance of a new trait in rapidly proliferating cells is explainable by clonal selection (Steele, 1979). The genetic transmission of such a trait does require, however, a vector, e.g. the provirus (Temin, 1976). Such a vector also might spread a useful new gene among the somatic cells that are not proliferating rapidly. If a beneficial mutation is copied as a RNA sequence or directly exported by the cell, it must be recognized from among other genes. A DMC, even if not shed itself, is set physically apart from its parent chromosome and, thereby, may be more easily distinguished from other genes available for RNA transcription. The DMC may also contain information on its proper location in the genome. This would explain the results of Nunberg et al. (1978) and prevent problems arising from improper insertion in the recipient genome

(Steele, 1979). By providing many identical gemmules of genetic information, complete with address, DMCs may be an agent of heritable somatic adaptation that selectively passes beneficial traits to future generations by way of the reproductive cells. Even if infrequent, such transmission of traits should speed and, in one sense, direct the course of evolution.

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