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EDITORIAL

Many mosaic mutations

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Steven Narod's latest Countercurrents contribution to *Current Oncology* discusses a new breast and ovarian cancer susceptibility gene known as *PPM1D*[1]. In this accompanying editorial, we put this exciting new finding in context.

MOSAICISM: WHAT IS IT AND HOW DOES IT HAPPEN?

Genetic mosaicism, as the name implies, indicates that the person is a mosaic—that is, composed of more than one genotype. At the time of diagnosis, all cancer patients are mosaics. They are mosaics because they comprise at least two distinct genomes: the genome they were born with, and the genome that they unwillingly acquired as a result of the initiation and growth of cancer. In fact, as discussed next, it may be that all humans are mosaics—but that some of us are more mosaic than others.

Normally, humans are derived from the product of a fusion of egg and sperm (the "zygote"). All cells that descend from that original founding cell are supposed to contain an identical nuclear genome—our personal genome. Traditionally, mosaicism is classified into two subgroups: somatic mosaicism and germ-line mosaicism. In a way, the latter is only a specialized version of the former: depending on when somatic mosaicism occurs, it can also lead to germ-line mosaicism. The key difference is that the minor genotype that generates a somatic mosaicism is not genetically transmissible to the next generation. By contrast, a germ-line (also called "gonadal") mosaicism can result in the occurrence of a genetic condition in an offspring of a clinically unaffected person. That situation occurs because the genetic mutations occur only in germ cells and not in the rest of the body. Hence, they remain clinically "silent."

Mosaicism happens because a mutation occurs at some point after the zygote is created. In general, the later in embryonic development that the mutation occurs, the more restricted in distribution the resulting phenotype is, because the cells derived from a mutated founding cell all carry its mutation. Many of the mutations may be neutral; some may not. They may thus confer some selective advantage (or disadvantage) to the cell and may therefore contribute to disease. If the mutation affects cell growth mechanisms, it may be "self-promoting" in the affected tissues, favouring (or hindering) expansion of the mutant population.

SOMATIC AND GONADAL MOSAICISM IN HUMAN CANCER

The example discussed by Dr. Narod is the most recent of a well-recognized phenomenon: that somatic mosaicism can result in non-transmissible, yet fully "genetic" cancers. The case of *PPM1D* includes several notable twists, not the least of which is that the mutations do not appear to be retained in the breast and ovarian cancers that are unequivocally associated with protein-truncating mutations in this gene. Thus, the mutations might act at a distance (possibly through some secreted, circulating factor) or might also be present in the tumour, but for some reason, are selected against. Other possible mechanisms await further exploration.

Thus far, these mutations have not been shown to be heritable. Mutations in other cancer susceptibility genes can occur mosaically, and in some situations, the deleterious mutations can be inherited. Perhaps the classic example is neurofibromatosis, which was long known to occur in segmental forms, whereby only parts of the body would be affected by the stigmata of neurofibromatosis type 1 (NF1) or type 2 (NF2). At least 10% of NF1 is thought to be attributable to mosaic mutations[2], some of which can also be present in the germline. Similarly, one third of all *de novo* NF2 presentations are somatic mosaics[3]. In those cases, the risk to offspring of an affected person is not zero; it has been calculated to be approximately 1 in 8[3].

Familial adenomatous polyposis is caused by germline mutations in *APC*. In about one third of cases, the mutation appears to arise *de novo,* because

there is no family history. Further investigation has revealed that up to one fifth of these apparently *de novo* cases are actually attributable to gonadal mosaicism, which in some cases has extended to include other tissues, but has not resulted in "full-blown" polyposis[4]. Mosaicism has in fact been reported for many cancer susceptibility genes[5,6]—most recently, for *BRCA1*[7]. Because the first case will always be sporadic, it is quite likely that these heritable mutations will remain unrecognized.

Cells that lack the usual complement of 22 autosomes and 2 sex chromosomes are called aneuploid cells. If aneuploidy occurs in the germline, it can result in well-known syndromes such as those of Turner (XO), Klinefelter (XXY), and Down (trisomy 21)—examples that illustrate the global impact of a varying number of chromosomes. If a variation in chromosome number does not occur in all cells in a person's body, the aneuploidy may be mosaic. Indeed, one such condition—mosaic variegated aneuploidy, resulting from biallelic mutations in the spindle assembly checkpoint gene, *BUB1B*—has been associated with pediatric and (rarely) adult tumours[8,9].

At least 1% of individuals are aneuploid or show copy-neutral loss of heterozygosity in their lymphocytes[10,11], and this percentage increases with age in people who are cancer-free (from 0.25% in a sample of people less than 50 years of age, to nearly 2% in those in their 70s). It is also significantly more likely to occur in people who later develop cancer[11]. In some cases, the embryonic origin of these structural abnormalities is evident in multiple tissues, including solid tumours of the adult, indicating the contribution of an embryonic genetic mosaicism to the adult[10]. Perhaps not surprisingly, the association between mosaic aneuploidy and cancer was strongest for leukemia[11], in which the odds ratio was increased by a factor of 35.

A most fascinating, but terrifying, human disorder in this area is Proteus syndrome, made famous by the film *The Elephant Man*. Because of the nature, distribution, and nonhereditary character of the illness, the underlying pathogenic mechanism was long postulated to be somatic mosaicism[12]. Recently, Leslie G. Biesecker's group showed that mosaic mutations in the *AKT1* oncogene underlie Proteus syndrome[13]. Interestingly, germline variants in *AKT1* have been associated with Cowden syndrome[14], some clinical features of which closely resemble Proteus syndrome.

SKIN AND BLADDER CANCER—A COMMON CAUSE?

AKT1 is not the only cancer-associated gene participating in disease through activating mutations that are also mosaic. Oncogenic mutations in *FGFR3, PIK3CA, HRAS, KRAS,* and *NRAS* (the same ones found in adult cancers) can cause epidermal nevus, a congenital proliferative keratinocytic skin lesion[15]. The extent of the epidermal nevus is indicative of the level of mosaicism (and possibly of the risk of cancer): A paradigm case report recently described a patient who first presented with urothelial bladder cancer at the very early age of 19 years, who subsequently developed two additional bladder tumours, and who had a congenital widespread epidermal nevus. An oncogenic mutation in *HRAS* was shown to be present in non-neoplastic cells from ectoderm, endoderm, and mesoderm, and in all tumours[16]. The spectrum of mosaicism has also been broadened to phacomatosis pigmentokeratotica. Mosaic *HRAS* mutations in stem cells able to differentiate into multiple cell types were again shown to contribute to both skin and bladder cancer[17].

MOSAICISM AND TUMOUR HETEROGENEITY

The foregoing observations point to the notion that there is no "personal genome." Rather, there are a myriad of "personal genomes" occurring in normal tissues, possibly contributing to disease. In the case of tumours, in which excessive growth of a clone takes place, distinct cellular populations become apparent. The genetic or genomic make-up of tumour reflects not only the history of the cells from which the tumour arose, but also the heterogeneity derived from increased proliferation rates and, often, DNA repair defects associated with cancer. A study reporting whole-genome sequencing of 21 breast cancers highlighted those issues[18]. That technique, together with development of the capability for single-cell whole-genome sequencing, will provide a detailed account of how heterogeneity contributes to neoplastic and non-neoplastic diseases alike.

IMPLICATIONS FOR PATIENTS

An understanding of the implications of mosaicism in patient care is still far in the future. It is conceivable that mosaicism involving cancer genes will be more prevalent among people presenting with early-onset cancer in the absence of a family history of disease. As indicated earlier, this scenario could have implications for offspring. Because the skin is "right before your eyes," the presence of phenotypic mosaicism should call for increased awareness of cancer risk. In non-neoplastic diseases, there is much to be learned. Might genetic mosaicism contribute to plaque development in atherosclerosis? To islet cell dysfunction? To neuronal loss or cognitive defects? Recent advances in genomic technologies will certainly shed light on those questions in the near future.

CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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