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LETTER

# Broadening the spectrum of cancer genes under selection in human populations

There is an increasing accumulation of evidence showing that the frequency of many human diseases has been formed by evolutionary procedures. Siddiqui et al.[1] performed an amazing study published in this journal, showing that *SIGLEC12* gene expression is associated with advanced cancer progression in humans. They performed a multi-level experimental and statistical analysis. In a multi-tissue carcinoma array, the gene product was present in ~80% of tissues and only 35% in a set of normal epithelial tissues. Forced expression of the gene in a *SIGLEC12* null carcinoma cell line had the consequence of enriching the transcription of genes associated with cancer progression, especially those related with KRAS and YAP/TAZ pathways. Compared with chimpanzees, it seems that the human receptor Siglec12 has lost its ligand after the human/chimpanzee lineage split, but notably the ligand gene remained in the chimpanzee genome. The authors also found evidence, using the Fst and Tajima D statistics, that a *SIGLEC12* null allele in human populations, ranging from 38% in sub-Saharan Africans to 86% in native American populations, is under positive selection. They propose that the functional *SIGLEC12* gene is currently under an elimination process in human populations, since its encoded protein, for unknown reasons, activates carcinogenic pathways.

This study of Siddiqui et al.[1]adds to previous studies that showed significant evidence for the action of natural selection on cancer genes. All human populations have high incidences of cancer, but some have especially much higher risk for certain cancer types. Voskarides[2] has presented data showing that populations living in extreme cold environments and extreme high altitudes have the highest cancer incidence in the world. Linear regression analysis supports the fact that the cancer-cold association is a world-wide phenomenon. Analysis of 247 Genome Wide Association Studies (GWAS) showed that this association has a genetic base. Cancer genes and especially tumor suppressor genes were found to be under selection in Inuit, Eskimos and Alaska Indians. Genetic variants that contributed to the survival of humans in extreme environments are probably associated with cancer incidence today. A similar evolutionary process was revealed for human populations living at extreme high altitudes, like Ethiopians and Andeans (high cancer rates, tumor suppressor genes under selection). A supporting fact is that previous studies showed that p53 mutations causing cancer in humans were found to be significant for the survival of some mammal species in the Tibetan highlands. These results were published in 2004 and 2013 by two different research teams. They found that in three different rodent species living under extreme environmental conditions (cold, hypoxia), certain amino acids in two conserved p53 residue positions (R174, S106) render p53 unable to activate apoptosis pathways.[3,4] It seems that resistance to apoptosis, a carcinogenic trait, it's an advantage under certain environmental conditions. This is related to a special evolutionary process known as "antagonistic pleiotropy", first proposed by George Williams,[5] one of the most well-known evolutionary biologists of the past century. He suggested that genetic variants selected as beneficial for survival at young ages, may have a deleterious effect later in life.[6,7] Selection of deleterious variants in DNA repair genes (considered as one of the main classes of tumor suppressor genes in mammals) is vital for unicellular organisms escaping extinction. Bacteria, protozoa, and monocellular fungi become very resistant under stressful conditions (antibiotics, oxidative stress, nutrient limitation, and other) when carrying mutations in DNA repair genes like *MSH2*, *PMS1*, *RAD51*, and others.[8-11] When these genes malfunction, the mutation flow is increasing and so are the probabilities for a beneficial mutation to appear. Weak selection on certain traits (the trait here is mutagenesis rate) is called relaxed selection. When environmental conditions come back to normal, these mutations can be gradually decreased or eliminated from unicellular populations.[12]

Has this phenomenon remained conserved in multicellular organisms? Martincorena et al.[13] has found thousands of deleterious mutations in cells of healthy esophageal tissue from healthy individuals, in 14 well-known cancer genes. Further analysis showed that these genes are under strong positive selection. The two most mutated genes are *NOTCH1* and *TP53*, genes that are frequently found mutated in esophageal cancer. Similar findings were published afterwards for other human tissues.[14-16] Maybe we have to re-consider our beliefs about

deleteriousness of mutations in cancer genes. Our cells, especially those living under challenging conditions, probably accumulate deleterious mutations in cell cycle, apoptosis and DNA repair genes, in order to resist toxic agents and survive. There are also examples of genetic variants that appear to involve cancer risk and reproduction. Every biologist knows that mutations in the *BRCA1/2* genes can cause ovarian and breast cancer. Utah women carrying pathogenic mutations in *BRCA1/2* genes and living under natural fertility conditions (born before 1930) had more children, shorter interbirth intervals, later age at last birth, and higher post-reproductive mortality than healthy controls.[17] This pattern was absent in women living in environments with modern contraception. Scientists trying to confirm these data, found mixed results.[18-20] Evidence of positive selection has been found only for the *BRCA2* gene.[21]

Summarizing, I think that it is presently a fact that cancer is an 100% evolutionary phenomenon. Modern studies allow scientists to realize the action of natural selection on cancer genes, cancer cells, individuals, and populations. Unfortunately, it is very hard for natural selection to eliminate mutations that cause cancer after the end of the reproductive age. It is even harder when cancer mutations have a dual effect by increasing adaptation. Taking examples from unicellular organisms,[12] it is possible that these deleterious mutations appear and disappear through a cycle procedure, that we poorly understand and is not yet proven in multicellular organisms. If it occurs, this cycle is spread over hundreds of thousands of years, thus it is difficult to study and confirm. Extreme events like famine, pandemics, radical climate change etc. can disrupt this cycle and mutation-selection equilibria may take too long to be stabilized. Maybe we have to find suitable animal models to simulate evolution in the laboratory to understand further these procedures.

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