Out of Africa – from skin to scrotum

Denys Wheatley, Editor.

Loss of skin pigmentation as early hominids left Africa and migrated North undoubtedly led to an increased risk of cancer. Since many cancers take decades to develop, with the majority arising and becoming life-threatening in post-reproductive years, the trade-off was good. In brief, human evolution by natural selection results in the retention of mutations that are generally beneficial, but some can incidentally have detrimental "side effects" – all life is a compromise.

The story goes that, to get the benefits in weaker sunlight of the uv radiation needed for vitamin D conversion, skin pigmentation was lost as mankind moved to temperature zones. But protection from the damaging rays of the sun was still needed. Sunburnt cells of fair skin activate p53, which, via its response elements, elicits KITLG production, stimulating melanocytes to synthesis melanin – in brief, a pathway of signalling returns the situation to square one. But genes are susceptible to mutations, many of which are lost that have no selective advantage, whereas some survive selection pressure, resulting in polymorphism. The smallest change that can occur in a gene is a (single) point mutation, where a one nucleotide has been substituted by another, and there seem to be many in p53 and its response elements.

p53 is one the pivotal proteins in controlling the fate of cells; it is a juggler than has so many response element associations with the genome that it can subtly twist cell behaviour from one direction to another, in this case from one extreme (survival and continued proliferation) to another (cell death by apoptosis). When malignant cells arise, wild-type p53 should direct them down the latter pathway. It follows that any mutation of p53 or its response elements might disturb this sensitive control over a multitude a genes, notably here the ones that induce apoptosis, particular in aberrant (potentially malignant) cells. Most of these changes that are detrimental to life are weeded out by natural selection, but the process is not fool-proof. The one in the focus of new research, KITLG p53 RE SNP, rs4590952, has slipped through quality control, and its positive selection and benefit in stimulating melanocytes is not without impunity. Using genomic analysis, Gareth Bond of the Ludwig Foundation Oxford (UK) Branch and Douglas Bell of the US National Institute of Environmental Health looked at almost 63,000 SNPs that might be related to cancer in which p53 has some operational control over transcription1. This particular variant of KITLG allows DNA damaged testicular stem cells to continue proliferating, the outcome being an increased risk of testicular cancer in white (Caucasian) men. With this recognizable marker, the development of appropriate tests indicating risk becomes a distinct possibility, as well as being indicative in prognosis of these cancers, and possibly giving some insight into treatment options.

This interesting finding follows on from Gareth Bond's work on several other polymorphisms in the last few years2,3. Clearly this is an Aladdin's if the group in Oxford can make similar associations along with other regulators of the cell cycle from the enormous number of SNPs being screened. But the story does not stop there, for this unwelcome side effect of KITLG p53 RE SNP, rs4590952 polymorphism remains to the detriment of the white men (Caucasians) because this variant is 4-5 times more common in them than Africans, which correlates with the incidence of testicular cancer, quoted as being only 25% as prevalent in Africans. So what about Inuit Indians, native American Indians, Mongols, Maoris and many other races; does skin pigmentation alone correlated here with testicular cancer? (Ironically, the one well pigmented area of the male body is the scrotum, which seldom gets sunburnt!) Some statistics can help, for the incidence of testicular cancer varies markedly worldwide (average 1.5 per 100,000 - which has doubled over the last 40 years4); but for different regions, in increasing order of magnitude (according CR UK5), the figures are: West Africa 0.2; North Africa 0.6; SE Asia 0.8; West Asia 1.5; Central Asia 3.7; Northern Europe 6.7; and Western Europe 7.8. I am in the last category; my risk of testicular cancer, while exceedingly slim, is in fact almost 40 times greater than for a West African, indicating many other mitigating factors.

References

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