Gain-of-function mutations: at a loss to explain molecules-to-man evolution

Jean K. Lightner

Evolutionists point to mutations as providing the raw material necessary for the onward, upward change they believe has occurred since life began. Mutations which affect an organism are often categorized into two basic types: loss-of-function mutations and gain-of-function mutations. A loss-of-function mutation is ‘a mutation that results in reduced or abolished protein function’. A gain-of-function mutation has been defined as ‘a mutation that confers new or enhanced activity on a protein’. A good understanding of these two types of mutations can be gained by examining mutations in the gene coding for a receptor located on thyroid cells and how these changes affect the control of thyroid hormone levels in the body.

A well designed pathway

The thyroid hormones, triiodothyronine ($T_3$) and thyroxine ($T_4$), affect essentially every tissue in the body. These hormones are necessary for maintaining an appropriate basal metabolic rate and are produced by the thyroid gland located in the front of the neck (figure 1). Thyroid stimulating hormone (TSH), a glycoprotein secreted by the pituitary gland in the brain, binds with the TSH receptor on the surface of cells in the thyroid gland. This initiates a series of biochemical events that result in the release of more TSH stimulation. This is an important part of the regulation pathway used by the body to maintain appropriate thyroid hormone ($T_3 + T_4$) levels. Thyroid stimulating hormone (TSH) is secreted by the pituitary and binds to its receptor on the follicular cells of the thyroid gland. This initiates a series of biochemical events that result in the release of more $T_3 + T_4$. Elevated $T_3 + T_4$ levels are detected by the pituitary, resulting in a decrease of TSH secretion. This is an important part of controlling hormone levels and maintaining homeostasis. Many other factors (not shown) also play a role in the regulation of $T_3 + T_4$.

At this point it should be apparent that the ‘enhanced activity’ mentioned in the definition has an unwarranted positive connotation. Activating mutations may result in more product, but they don’t result in something more valuable. Instead, there is a loss of control of a pre-existing biochemical pathway. Living things depend on being able to maintain homeostasis, or a balance. Although the pituitary responds to the high thyroid hormone levels by decreasing TSH release, it has no effect on the constitutively active receptor. The excess thyroid hormone doesn’t ‘enhance’ anything, it causes disease.

Figure 1. A highly simplified schematic showing the negative feedback loop used by the body to maintain appropriate thyroid hormone ($T_3 + T_4$) levels. Thyroid stimulating hormone (TSH) is secreted by the pituitary and binds to its receptor on the follicular cells of the thyroid gland. This initiates a series of biochemical events that result in the release of more $T_3 + T_4$. Elevated $T_3 + T_4$ levels are detected by the pituitary, resulting in a decrease of TSH secretion. This is an important part of controlling hormone levels and maintaining homeostasis. Many other factors (not shown) also play a role in the regulation of $T_3 + T_4$.

Other mutations within the gene for this receptor result in a ‘gain-of-function’. In this case the receptor is constitutively active, or ‘switched on’ even when TSH is not present. Many of these mutations have been identified, yet most of these are not heritable (germ-line) but somatic mutations. Most commonly, activating mutations are found in thyroid nodules (over 2 dozen different mutations, some identified in more than one individual) which develop from long term iodine deficiency or exposure to goitrogens. Activating mutations have also been described in cases of sporadic hyperthyroidism and thyroid cancer (carcinoma—see figure 2).

Loss-of-function mutations

One important part of this regulatory pathway is the TSH receptor found on the surface of cells in the thyroid gland. Not surprisingly, mutations within the gene coding for the TSH receptor can create problems for the body in controlling thyroid hormone levels. A number of loss-of-function mutations have been identified which impair the receptor to different degrees and thus result in varying degrees of hypothyroidism. Like most loss-of-function mutations, these mutations are generally recessive. This means that clinical signs are typically observed only when both genes (one being inherited from each parent) for the receptor carry such a mutation. There are around 20 different loss-of-function mutations in this gene that have been described in the literature.

A gain of … what?

Several diseases exist where the body is unable to properly regulate thyroid hormone levels in the blood. Hypothyroidism occurs when there are insufficient levels of thyroid hormone and is often associated with signs of intolerance to cold, lethargy, weight gain and cool, dry skin. Hyperthyroidism is caused by excessive thyroid hormone and signs may include rapid heart rate, intolerance of heat, weight loss and fatigue. At this point it should be apparent that the ‘enhanced activity’ mentioned in the definition has an unwarranted positive connotation. Activating mutations may result in more product, but they don’t result in something more valuable. Instead, there is a loss of control of a pre-existing biochemical pathway. Living things depend on being able to maintain homeostasis, or a balance. Although the pituitary responds to the high thyroid hormone levels by decreasing TSH release, it has no effect on the constitutively active receptor. The excess thyroid hormone doesn’t ‘enhance’ anything, it causes disease.
In addition to controlling the output of thyroid hormone, the TSH receptor is part of a second biochemical pathway that regulates the growth and development of cells in the thyroid gland. Mutations in the genes coding for such proteins can often lead to the development of cancer.

A new, but not improved, function

One gain-of-function mutation is different and results in a protein with a ‘new function’. In this case the mutation alters the receptor so it responds to human chorionic gonadotropin (HCG). HCG is a hormone that increases early during pregnancy to help maintain the pregnancy. While HCG naturally stimulates the TSH receptor to some degree in early pregnancy, the mutation causes the receptor to be so sensitive that overt gestational hyperthyroidism develops. Again, the pituitary responds to increased thyroid hormone by decreasing TSH, but since the receptor is responding to HCG this doesn’t solve the problem. When a protein loses its specificity and becomes involved in reactions it wouldn’t normally be involved in, it has a ‘new function’. This is often referred to as promiscuous activity. Even though very rarely a protein with promiscuous activity may prove beneficial under special circumstances, still the loss of specificity represents a downward change in the genome. It is impossible to build complex pathways with appropriate feedback mechanisms by randomly introducing errors.

Conclusion

It is worth noting that mutations produce new alleles (variant forms of a gene) and certainly add variety. However, molecules-to-man evolution requires the generation of new information to build new, complex, interdependent biochemical pathways. Despite the deceptive wording found in the gain-of-function definition, there is no increase of information or improvement of biochemical pathways. Without a mechanism for developing such pathways, evolution is nothing more than a myth. Instead, what we observe fits exactly with what we would expect if the Bible is true. Living things are very well designed. Errors introduced by mutations do not build new, well-integrated biochemical pathways; instead they often cause disease.

References

4. The control of thyroid hormone level in the body is actually far more complex than this. The body must also respond to external temperature and other internal signals to maintain proper hormone levels.
9. A dozen different heritable gain-of-function mutations have been described out of nearly 9 dozen different gain-of-function mutations in the TSH receptor gene. Generally, loss-of-function mutations are more common, but that doesn’t appear to be true of this particular gene when somatic (non-heritable) mutations are included (ref. 7).
10. Goitrogens are substances which suppress thyroid function. Examples include calcium and fluorides in drinking water and compounds found in certain foods such as cabbage, casava and brussel sprouts; <www.fpnotebook.com/END197.htm>, 9 September 2005.
11. Elsewhere, the same online dictionary describes gain-of-function mutations as conferring ‘an abnormal activity on a protein’. This is accurate; <www.medterms.com/script/main/art.asp?articlekey=39612>, 9 September 2005.
12. Rodien, P. et al., Familial gestational hyperthyroidism caused by a mutant thyrotropin receptor hypersensitive to human chorionic gonadotropin, New England J. Medicine 339(25):1823–1826, 1998. This is distinct from a molar pregnancy, where hyperthyroidism is induced by excessively high concentrations of HCG.
13. Lightner, J., Special tools of life, <www.answersingenesis.org/docs2004/0512tools.asp>, 9 September 2005. The three mutations described in this web article would be defined as gain-of-function mutations. Although the second mutation, resulting in a loss of specificity in ribitol dehydrogenase, effected a greater loss of activity toward ribitol than gain of activity toward xylitol, it is still by definition a gain-of-function mutation (due to its activity toward xylitol). While none of these mutations truly increase information within the genome, these types of mutations likely have played some role in animals adapting to new, harsh environments since the Fall. Notice that they enable the organism to survive under unusual conditions, yet significantly decrease the fitness of the organism under most circumstances.