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The evolution of gene regulation: How microbial neighbors settle differences

May 26 2009

Supply and demand could be a governing principle even at the genetic level, because most genes are only expressed when needed. Biologists at the Ludwigs-Maximilians-Universitat in Munich, Germany, show that in microbes evolutionary factors determine which regulation mechanism will regulate a given gene.

Even microbes are governed by the principle of supply and demand - at least at the genetic level. Not all of their gene products, the blueprints for proteins, are required at all times. That means most of their genes only become active when they are needed, as is the case in higher organisms. In the simplest case, a transcription factor will activate the gene in question at the right time.

Genes that are regulated in a somewhat more complex manner, on the other hand, are kept inactive by a repressor that is removed only when the gene is needed. Which of these two regulation mechanisms will develop is a question of demand, along the lines of a "use-it-or-lose-it" principle: if genes are frequently active, then, as a rule, they will be directly induced. Genes that encode more rarely used proteins, on the other hand, tend to be kept inactive by repressors. LMU physicist Ulrich Gerland and Professor Terence Hwa of the University of California have now demonstrated using computer simulations and theoretical analyses that another - indeed opposing - principle also comes into play: "wear-and-tear".

According to this principle, direct activation can lead to harmful changes. "Which of the two principles prevails depends on evolutionary criteria such as the population size and the periods over which environmental changes take place," says Gerland. "Our study may serve as a useful basis for more detailed studies of the evolution of regulatory systems." (*PNAS* Early Edition, 22 Mai 2009)

Up until the middle of the 20th century, biochemists spent most of their efforts studying metabolism, i.e. obtaining energy from food. Less importance was given to the - technically inexplicable - question of how proteins were regulated as a response to internal and external signals. The biology of regulation only came into its own as an independent research field when technical progress opened the window to scientific analysis of DNA, the carrier of genetic traits, and to the synthesis of proteins, the most important functional elements of the cell. It quickly became clear that complex and diverse regulation mechanisms adapted the genetic activity of cells to internal and external conditions - even in microorganisms.

It is known, for example, that the intestinal bacterium Escherichia coli in the digestive tract of young mammals can break down lactose, the sugar abundant in mother's milk. To do this, the bacterium produces the enzyme lactase - but only if lactose is actually present. Most of the time, however, lactose is not present. At these times, the gene that encodes the lactase enzyme is blocked by a repressor. Only one key fits the lock to this protein, to detach the repressor from the lactase gene: a lactose molecule, as a single, unmistakable sign that this sugar is present and now available as food. Other genes, however, are regulated without the use of repressors: these genes are directly activated by a transcription factor that binds to them.

These are only two simple examples of mechanisms that regulate gene activity, and they are functionally equivalent. "The question was raised long ago as to whether nature's choice in favor of one of the two mechanisms is only random, or whether there are specific criteria," reports Gerland. "Studies have shown that the demand for a gene product is a decisive factor: it is mostly genes whose proteins are required most of the time that are directly activated. Proteins such as lactase, on the other hand, which are only used some of the time, tend to have genetic codes that are only released from their repressor when needed." The "use-it-or-lose-it" principle was proposed to explain this, which demands the frequent use of regulation factors because they would otherwise be subject to damaging effects.

Using computer simulations and theoretical calculations, Gerland and Hwa have now demonstrated that a second - even opposing - principle also comes into play: "wear-and-tear". Its name reflects the fact that constant use of regulators can also lead to detrimental consequences. The two researchers therefore investigated whether other factors that can affect the evolution of microorganisms play a role. "Our results clearly show that both principles are valid, even though they are actually contradictory," Gerland says. "In this conflict between maximal and minimal use of the regulators, other criteria do in fact come into play: the population size and the periods over which the environmental changes stretch."

Genetic regulation in small populations existing in an environment that only slowly changes is governed by the "use-it-or-lose-it" principle, with maximal use of the regulation proteins. In the opposite case, however, it is more "wear-and-tear" that comes into play with minimal use of the proteins. "The evolution of regulatory systems is still barely understood," reports Gerland. "So far, appropriate theoretical methods have also been largely lacking. But the time-dependent selection shown in our example may now prove to be an important factor in regulatory development. Many questions are still open, and our results will hopefully prompt further investigations."

More information: "Evolutionary selection between alternative modes of gene regulation", Ulrich Gerland and Terence Hwa,
PNAS Early Edition, 22 May 2009

Source: Ludwig-Maximilians-Universität München