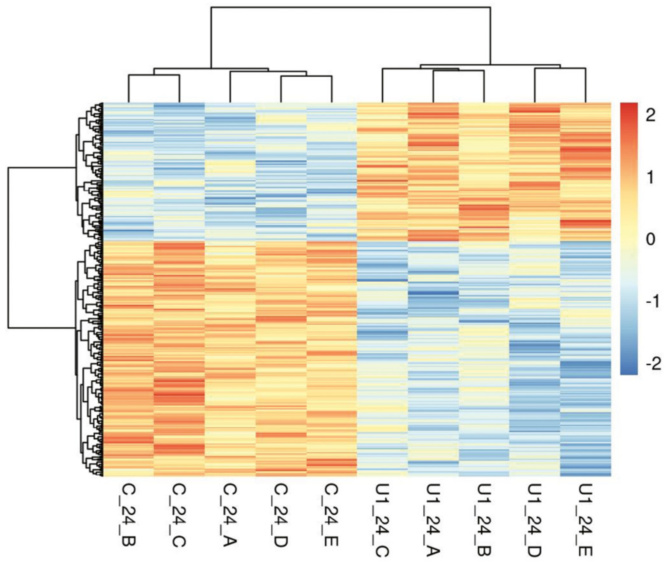
Florian Böhl's research work at Creavis focuses on methylation patterns on DNA that point toward the origin of an individual living organism

THE PATTERN ON THE GENES

How do environmental factors influence genes? The science of epigenetics addresses this question. At Evonik, a team led by Florian Böhl has developed a process that can precisely determine the biological age of chickens

TEXT **SINA HORSTHEMKE**



Environmental influences cause methylgroups to bond to or uncouple from the DNA strand. Depending on their number and distribution, this creates a very characteristic pattern

With its multitude of colored fields juxtaposed in a seemingly chaotic arrangement, the computer monitor of Dr. Florian Böhl looks like a patchwork quilt. In fact, the colored fields on a white background show millions of measurement results obtained from the DNA strand of a chicken. "I used to think that in the field of animal diagnostics everything had already been discovered," says Böhl, who holds degrees in biology and business management and worked in Sweden, Germany, England, and Switzerland before joining Creavis six years ago. At this unit, Evonik is transforming future-oriented technologies into new business activities. "However, after I took a closer look, I discovered the uncharted territories on the map. That activated my natural affinity for scientific research."

The decoding of the human genome 20 years ago was a sensational achievement. It seemed as though every aspect of genes was now known. But that was a mistake. Today it's clear that DNA is not the only factor that determines what a living organism looks like and how it behaves. The organism's environment has an influence on its genes—and thus on its appearance and behavior, as well as the speed at which it ages. This influence is so strong that these changes are passed down to subsequent generations. Scientists call this phenomenon epigenetics.

Some researchers are investigating the epigenetics of human beings, while others are decoding the DNA of crayfish or wild animals. Florian Böhl was intrigued by chickens. Together with his team and colleagues at various locations, Böhl, who is now 49, is decoding the epigenetic patterns of this species. His goal is to develop new technologies at Creavis that help to improve an- →

Evonik uses the infrastructure of the German Cancer Research Center in Heidelberg for some of its methylome analyses. This device reads out chips containing DNA samples

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PROFESSOR FRANK LYKO,
HEAD OF THE DIVISION OF EPIGENETICS OF THE GERMAN CANCER RESEARCH CENTER

imal welfare, make agriculture more sustainable, and optimize meat production. “Healthy chickens give better meat,” says Böhl. “For that reason alone, the animals should live as well as possible before they are slaughtered.”

IN THE BEGINNING WAS THE CHICKEN

There’s a good reason why Böhl is focusing on chickens: Poultry and pork are the two most popular varieties of meat worldwide. On average, every human being consumes 15.6 kilograms of poultry and of pork annually, but only 9.1 kilograms of beef. In 2019, 25.9 billion chickens were kept as livestock, 80 percent more than in 2000. “People all over the world eat chicken,” says Böhl. “By contrast, it’s hard to sell a pig in predominantly Muslim regions or to sell a cow in India.” An additional factor is efficient feed conversion: A chicken needs much less feed than a cow, for example, to produce the same volume of meat. “Besides, chicken meat is low in fat and healthier than the meat of many other animals,” Böhl adds.

Healthy nutrition is a current trend. And Böhl was already wondering years ago how it could be possible to help shape this trend in livestock farming. But how can we find out how well a chicken is doing at any given moment? By measuring the level of stress hormones in its blood? Böhl believed that would not be sufficiently precise. He thought back to his time at Cambridge University, and suddenly he had an idea. “As a cell biologist, I was investigating how genes could be shut down or activated,” he says. Böhl, who had originally conducted research with yeast and fruit flies, decided to apply the knowledge he had gained to broiler chickens—in the special field of epigenetics.

As early as the 19th century, the French biologist Jean-Baptiste de Lamarck realized that living organisms obviously transmit acquired characteristics to their descendants. Back then, no one took him seriously; this idea contradicted the recently discovered science of heredity, and Lamarck himself could not explain his theory with sufficient plausibility. The concept only picked up speed shortly after the turn of the millennium, when researchers were suddenly able to analyze DNA. Initial studies revealed that the experiences of forebears had an effect on the genes of their descendants. Elizabeth Blackburn, who received the Nobel Prize for Medicine in 2009, was one of the first researchers to investigate the hypothesis that stress alters the genome.

The monitor shows the methylation patterns that provide information about the biological age of an organism

SWITCHES ON THE DNA

Today it’s a recognized fact that experiences such as famine, illness, and trauma really do have an influence on the genes. They cause either the attachment or the uncoupling of chemical markers on the DNA strand (see the diagram on pages 44/45). These markers, which are called methyl groups, switch genes on and off, because they provide orientation for the enzymes that are responsible for reading the information in the genome and turning it into physical reality. Depending on whether methyl groups are adhering to the DNA strand or not, the enzymes receive the message “Read this!” or “Don’t read this!” The environment does not change the genes themselves, but it does alter the way they are interpreted and thus their activity.

In the field of epigenetics, the aim is not to influence DNA. On the contrary, epigenetics is an observational discipline. Epigeneticists look very closely at the methylation pattern on the DNA—in other words, the number and the distribution of the attached methyl groups. The pattern enables them to infer how environmental influences have changed the genes’ activity in the course of a lifetime. Only a few years ago it became clear that the process is dynamic and that it plays a role in the genesis of illnesses such as cancer, for example. Researchers have also realized that there are temporary as well as lasting epigenetic changes. Because the methylation pattern reveals so much about a living organism, scientists call it the methylome or the epigenome, analogously to the genome.

THE ANCESTORS’ FAMINE

Epigenetics is known as the link between the environment and the genes. It is the field of biology that deals with a living organism’s physical appearance. “We look different at various points of time during our lives—depending on how old we are,” says Böhl. “But this cannot be explained in terms of the genes, because they always remain the same. It can only be explained via epigenetics.” Epigenetics reveals the biological age of a human being, which depends, among other things, on whether the person has had lifelong healthy nutrition, smoked heavily, practiced sports or frequently drunk alcohol.

Epigenetics also helps to explain why overweight and diabetes are strongly increasing in many countries that used to be underdeveloped. In phases of famine, the individuals who can store energy effectively have the best chances of survival. If sufficient food then suddenly becomes available, their descendants gain weight faster than the average. In animal experiments, the descendants of underweight mice had a higher risk of diabetes even two generations later.

AS CHEAP AS A T-SHIRT

In order to run comparisons of the epigenome of chickens, Böhl’s team at Evonik reads out 26 million points from each set of chicken DNA. It sounds complicat- →

Evonik researcher Florian Böhl (left) with his one-time fellow student Frank Lyko from the German Cancer Research Center

ed, but it's not only simpler than previous methods but also much more precise and cost-efficient. "The analysis costs no more than a T-shirt," says Böhl. Nonetheless, the volumes of data are gigantic—they can only be evaluated by an algorithm supported by artificial intelligence. "We derive knowledge from this data and make it possible to gain insights that previously did not exist," he adds. Because DNA cannot be seen by the naked eye, the researchers visualize the chaotic mass of data as a "heat map"—the diagram that looks like a patchwork quilt.

The initial conclusion that Böhl's team reached after analyzing the chicken methylome was only an incidental finding, but it was a scientific sensation. The methylome of the sperm cells showed that in terms of their evolution birds are more closely related to platypuses and echidnas than to reptiles, fishes, and mammals. Conversely, primitive mammals such as the echidna are not as closely related epigenetically with the mammals of today as was previously believed. "We were totally fascinated by this discovery," says Böhl. "It explains why raising chickens is more difficult than raising mammals. It's because the DNA methylation in the germ cells—that is, the sperm and egg cells—functions differently."

AN EPIGENETIC CLOCK

Most importantly, however, the epigenome researchers used the data they had gained from chicken tissue to develop an "epigenetic clock" for chickens. This is how it works: An intelligent algorithm analyzes the methylation pattern on a chicken's DNA, learns related information such as its age or the conditions under which it is kept, and then becomes smarter with every additional data set. If the algorithm is fed with new DNA, it compares this DNA with the knowledge it already has and thus enables reliable statements about aspects such as the origin of the meat. That's because every type of farming leaves behind a characteristic pattern that can be created only in a certain environment.

In addition, the methylome makes it possible to pinpoint the biological age of the chickens. "Nobody has ever been able to do that before with such precision," says Böhl in praise of his team's results. For human beings, with their average lifespan of about 80 years, exact predictions can be made to within three or four years, but Böhl can precisely define what the methylome of his chickens will look like a day and a half from now. That enables him to make precise statements about the condition of the animals. In large populations of animals, this is important information. After all, the health of broiler chickens is crucial for their well-being and ultimately for the quality of their meat.

To make sure that the "chicken clock" could be used as a health check, Böhl's team analyzed the methylome of chickens with a gut infection. "It showed that the immune system correlated with our measurements," he says. The inflammatory reaction changes the methylation—and that too is a new discovery. Its main advantage is that this molecular biology tool can be used for every kind of tissue. "We can make the measurement in the animal's loin, its leg or a part of its gut—on principle, it doesn't matter where," Böhl says.

One of the most important partners in Böhl's farflung network is Professor Frank Lyko, a former fellow student of his at Heidelberg University, who is now the head of the Division of Epigenetics of the university's German Cancer Research Center (DKFZ). At some point, Böhl told his former fellow student about the chicken epigenome. Even though at first sight this topic has little to do with research on human cancer, Lyko was interested. The two scientists' initial joint experiments eventually grew into close cooperation. Böhl uses the infrastructure of the DKFZ, and Lyko benefits from Böhl's findings.

Today, unlike a few years ago, we know that cancer is triggered not only by mutations in DNA but also by other factors, says Lyko. Now, he explains, it's clear that "epigenetic mutations on the DNA, which are known as epimutations, also play a role." Lyko adds that authorization has been received for initial cancer tests based on epigenetic markers, and even for the first medications that work by means of epigenetic mechanisms. "The way that the environment interacts with the epigenome is a significant element of our understanding of cancer, but it's not easy to investigate it in human beings," he says. As a result, animal models are playing a major role—especially models of animals that are genetically homogeneous and grow up under standardized conditions, but are nonetheless subject to a variety of environmental factors. Chickens fulfill these requirements.

WHEN DREAMS BECOME REALITY

What Lyko appreciates about his former fellow student Böhl is that he is equally attentive to science and business. "He can conduct scientific discussions at a very high level, and at the same time he's capable of developing a business idea out of it," he says. Böhl admits that "something's always at work" inside his head. He says he's constantly thinking about possible applications for his areas of work. "It's important to transform ideas into reality so that they can provide benefits," says the researcher. And even though it will take some time for the epigenetic clock to be used in the meat industry, he envisions huge opportunities. He says that the long-term goal is to work together with livestock farmers to keep a closer eye on their animals' health and thus take meat production to a new and more sustainable level. That applies to chicken farming as well as cattle breeders and aquacultures.

Moreover, consumers would be able to receive even better information about fish and meat in the future. Where did this salmon live before it landed on my grill? Was this pig healthy before it was slaughtered? And were these chicken wings really produced as sustainably as the packaging claims? The epigenome reveals something that is more important today than ever before for enlightened consumers: transparency about the food on their plates.

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>
> DR. FLORIAN BÖHL, HEAD OF DIAGNOSTICS AND NEW BUSINESS DEVELOPMENT AT EVONIK

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