German Genetics Society Meeting 2009: Session I

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The second guest post from fellow science blogger Alex Knoll reporting from the German Genetics Conference currently held in Cologne.

The first session was all over the place in terms of topics.

Starting off the meeting, Linda Partridge from the Institute of Healthy Ageing in London and the Max Planck Institute for Biology of Ageing in Cologne told us about the Genetics of Ageing.

Looking back, there has been a linear increase of life expectancy in humans for a rather long time now, with about 2.5 years added every decade. That comes down to about 6 hours of increased life expectancy per day!

While there is no single cause for ageing, it is nonetheless controlled by genes and can evolve. And although life expectancy is generally correlated with the body size of animals, there are several exceptions like the little Brandt's bat that can live for 38 years, and there are also some organisms that don't seem to age at all!

At first it was thought that the research of ageing in model organisms would not be too relevant for the understanding of human ageing, because there were many unique pathways in the different animals. Interestingly, in many model organisms like the worm Caenorhabditis elegans, the fly Drosophila melanogaster and also the mouse, the insulin pathway plays a big role: When components of this pathway are knocked out, the lifespan of the animal increases. This means the healthy lifespan, the organisms spend more time in the prime of their life instead of just being old and sick for a longer time. Even in humans, population genetics studies found homologues of some of these genes as candidates. The implication of the insulin pathway fits nicely to earlier observations of dietary restriction: If you put an organism on a diet with less calories than it usually eats, it will live longer. This is rather easy to do in the fly: just dilute the sugar solution it eats. This way it was possible for the people in Linda Partridge's lab to compare putative genes implicated in ageing with dietary restriction.

They then asked the question: how deeply is the genetics of ageing conserved between organisms? By using comparative microarray studies with worm, fly

and mouse, they were able to identify functional categories of genes that are up- or downregulated in ageing.

Frank Grosveld from the Erasmus Medical Center in Rotterdam talked about a systems biology approach to understand the transcriptional regulation of globin genes in the mouse. During the development of red blood cells, several large multiprotein complexes act as transcription factors and bind to regulate the proliferation and differentiation. With a systems biology procedure, Frank Grosveld's lab tried to find and identify binding partners of known transcription factors during early and late stages of erythrocyte differentiation. For example, GATA1 makes several different complexes that very early on repress non red cell genes to prime the lineage, later another complex with GATA1 represses proliferation as a requirement for differentiation.

Interestingly, the globin locus that is expressed during erythrocyte development, lies in between many olfactory genes. With the help of several proteins binding at a number of regulatory regions, the structure of the chromatin is altered so that these olfactory genes are looped out and the components of the globin locus come to lie near each other. This also enables long range interactions of elements that are farther away, sometimes several megabases! The chromatin loops also change depending on the tissue: the globin locus is expressed in the fetal liver, and there it contacts other actively expressed genes. In the fetal brain, on the other hand, the globin locus is inactive, and it contacts mostly other inactive genes. The looping can even be shown microscopically by measuring the volume of the the globin locus. In expressing tissue the volume decreases, which indicates extra looping.
Another interesting aspect of Frank Grosveld's work touches blood disorders like thalassemia and sickle cell anemia. These result from defects in the beta-globin gene and are hard to treat. The idea here is great: in fetal tissues, the gamma-globin genes are expressed, but they are repressed perinatally. They have been able to identify a handful of proteins that are responsible for this repression in mice, and downregulation of these proteins leads to an upregulation of gamma-globin expression and a downregulation of beta-globin. These repressors are now novel targets to develop a new type of treatment for these anemias.

Finally, Marjori Matzke from the Gregor Mendel Institute in Vienna spoke about epigenetics in plants. Specifically, she told us about her research into RNA-dependent DNA methylation (RdDM) as a way to regulate transcription in plants, where not only repeats and other such elements are processed, but also single genes. This is done via small RNAs and the action of the two RNA polymerases PolIV and PolV. These are related to the standard RNA polymerase PolII, but possess different C-terminal domains that are responsible for their functional diversification. After 24-nt long siRNAs are produced, they lead to de novo methylation and thus inactivation of target sites with the help of PolV and other factors. From this inactivated locus then further siRNAs are produced with PolIV to keep the methylated state. Using a silenced GFP expression system, the Matzke lab searched for mutants with defects in RdDM, and found several

until now.
RNA-dependent DNA methylation as a further method of transcriptional regulation in the cell, for example for stress responses in plants that can't run away from the stress arrived at an interesting time in plant evolution. The group of flowering plants appeared rather abruptly in the fossil record, prompting Charles Darwin famously to speak about an 'abominable mystery'. PolV and other factors involved in RdDM are only to be found in flowering plants, which could let one conclude that the newly evolved epigenetic plasticity played at least a part in the evolution of this successful group.

The first day of the meeting ended with a public lecture by Peter Propping from Bonn in Germany. His talk in German was about the history and future of human genetics ("Der Mensch und seine Gene in der Welt von morgen"). He started by telling us about the problematic standing of human genetics in the middle of the last century, mostly because of concerns stemming from the earlier decades with eugenics, sterilizing and killing people because of genetic concerns.

The big successes then came with the research into monogenetic diseases, which firstly were reached by methods such as positional cloning. Now is the time to study multifactorial diseases, which are much harder to tackle; here we have many genes which only contribute a small amount to the phenotype, and environmental effects contributing as well. A nice example of a new kind of genetic defect are copy number variants, where a sequence is repeated a different number of times between individuals. But this is not well understood for now, because the same CNVs can be found in diseased patients, but also in healthy people.

In the future a lot of work will be done with next generation sequencing, which will hopefully put a lot of data into the hands of the researchers. On the other hand, this means that a lot of money will be spent – a criticism that can be heard already now.

Another part of his talk was about the possibilities of and problems of prenatal screening. It was rather surprising for me to hear that in Germany in about 10% of pregnancies a screening is done, mostly to look for chromosomal mutations like trisomy 21 (that is responsible for Down syndrome)! Pre-implantation diagnostics in the course of in vitro-fertilization, however, is not allowed in Germany, which lead to a PID tourism into other European countries.

Finally Peter Propping also talked about the new law for genetics diagnostics in Germany, which has some problems. For example, genetic analysis is defined by methods in the law, which leads to the curious case that even simple biochemical work such as blood group determination falls under the regulations of the new law!