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EDITORIAL

150 years of Johann Gregor Mendel's "Versuche über Pflanzen-Hybriden"

Uwe Hoßfeld[1,2] · Hans-Jörg Jacobsen[3] · Christoph Plass[4] · Benedikt Brors[5] · Wilfried Wackernagel[6]

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In 1866, J. G. Mendel published his seminal work on what is known today as the Mendelian rules in genetics (Mendel 1866). With this contribution, he ignited the discipline of genetics. Historically, his finding that traits of parental organisms are passed to the offspring by an inevitable and predictable mechanism via "elements" (genes) was premature. When Mendel's discovery finally entered the scientific world with a delay of more than three decades, it then had a huge impact on science and society. The agricultural breeding of plants and animals was put on a new productive level. Consequences for medical considerations and social and political movements followed soon. A deeper understanding of evolutionary processes was encountered and the pass was laid for the rise of molecular cell biology. To celebrate the 150th anniversary of Mendel's fundamental publication, a compact symposium with four keynote speakers was held at the Carl-von-Ossietzky University of Oldenburg in July 2016. The aim was to reevaluate the history of events that led to Mendel's work and its spread in science, and to highlight current concepts in plant genetics, non-Mendelian genetics (epigenetics) in cancer research, and personalized medicine, all of which find their foundation in large in Mendel's observations.

According to the popular view presented by almost all textbooks of genetics and schoolbooks, Mendel's rules were "rediscovered in 1900 simultaneously and independently" by the three botanists Hugo de Vries (1848–1935), The Netherlands, Carl Correns (1864–1933), Germany, and Erich von Tschermak-Seysenegg (1871–1962), Austria-Hungary. Dr. Uwe Hoßfeld summarized in his keynote ("Mendel reloaded: the "rediscovery" of Mendel's rules around 1900") that since the 1950s, research in history of science increasingly questioned this view based on the analysis of multiple sources that shed light on the individual research programs and the ideas of the three scholars. As a consequence, the youngest of them, Erich von Tschermak-Seysenegg, was later excluded from the rank of a "rediscoverer". His original understanding of Mendel's findings and explanations in 1900 had limited validity both in conceptual and terminological terms. The failure resulted from (1) that he was not able to draw any generalization from the data he obtained in his crosses with garden peas and (2) that he did not attempt to explain his results within an appropriate framework. A new and further aspect to this is the identification of his elder brother, the professor of

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✉ Christoph Plass
c.plass@dkfz.de

✉ Wilfried Wackernagel
wilfried.wackernagel@uni-oldenburg.de

1 Abteilung Biologiedidaktik, Biologisch-Pharmazeutische Fakultät, Friedrich-Schiller-Universität Jena, Am Steiger 3, 07743 Jena, Germany

2 Faculty of Technology, Management and Innovation, ITMO University, Chaikovskogo st. 11/2, Saint-Petersburg 191187, Russia

3 Institut für Pflanzengenetik, Naturwissenschaftliche Fakultät, Leipnitz-Universität Hannover, Herrenhäuser Straße 2, 30419 Hannover, Germany

4 Abteilung für Epigenetik und Krebsrisikofaktoren, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

5 Abteilung für Angewandte Bioinformatik, Deutsches Krebsforschungszentrum, Im Neuenheimer Feld 280, 69120 Heidelberg, Germany

6 Institut für Biologie und Umweltwissenschaften, Fakultät Mathematik und Naturwissenschaften, Carl-von-Ossietzky-Universität Oldenburg, Ammerländer Heerstraße 114-118, 26129 Oldenburg, Germany

physiology in Halle, Germany, and later in Prag, Bohemia, Armin von Tschermak-Seysenegg, as the *spiritus movens* for most of Erich's studies at that time. These included the already mentioned artificial pea crosses and their relation to Mendel's fundamental paper that was known to Armin (Simunek et al. 2011a, b). Evidence from correspondence is also provided that the "rediscovery" was less independent as generally assumed, since the two brothers knew of the attempts of de Vries and Correns, and Erich was the last of the three to engage in artificial crosses (Simunek et al. 2011b). In fact, the myth of the three "independent and simultaneous rediscoverers" was enforced and spread by Armin over decades in numerous publications, including a broadcast lecture in 1939 (Simunek et al. 2011b) probably to support the academic career of his brother. Although the correspondence between the brothers is clearly incomplete, information therein can help provide more detailed answers to questions pertaining to degrees of success in interpreting Mendel's work in the crucial period of 1899–1901.

The rediscovery of Mendel's groundbreaking paper more than 100 years ago transformed plant breeding from an intuitive endeavor to a modern science and boosted plant breeding dramatically. Yields and yield potential in almost all crop plants constantly went up and peaked when the ideas of the green revolution reached the farmers worldwide in the 1970s. Dr. Hans-Jörg Jacobsen explained in his paper ("Plant genetics and modern plant biotechnology") that at the end of the 1970s, it became clear that the conventional breeding has its limitations as it is restricted to the crossable gene pools of our crop species and their near relatives. In addition, the sobering results of almost 30 years of mutation breeding made clear that plant breeders need novel tools to solve the upcoming problems in feeding an ever growing world population in a more sustainable way, i.e., with lower inputs in pesticides, fertilizer, and water. Therefore, another groundbreaking discovery, namely solving the mechanisms of *Agrobacterium tumefaciens*-dependent tumor formation in plants opened new avenues for plant breeders (Joos et al. 1983). Using "disarmed" Agrobacteria enabled scientists to functionally move genes from genetically non-compatible species and also from other kingdoms into plants, resulting in genetically modified organisms (GMOs). In particular, resistance and quality traits were improved in several crop plants. As we know since 2015 that this type of "horizontal gene transfer" is a natural process and a driver of natural evolution (Kyndt et al. 2015), it is surprising that some western societies, triggered by some non-governmental organizations (NGOs), are so hostile to plant genetic engineering. While most of the approved transgenic crops are herbicide and/or insect resistant and have already significantly contributed to the reduction of pesticide use (Klümper and Qaim 2014), a number of interesting projects regarding transgenic plants with improved drought or salt tolerances are either in field trials in the US or Canada or, as it is the case in Germany, are sitting on the shelves of public labs, waiting for approval—waiting for ever? The worst case is the "Golden Rice" scenario, where anti-GMO-NGOs are preventing the application, just because they do not want any success story for GMOs (http://goldenrice.org).

The field of genetics has also spread into non-Mendelian genetics with a prime example of epigenetic alterations, which do not change the genetic code, but strongly influence gene expression patterns. Patterns of epigenetic modifications are highly specific for specific regions in the genome and define promoter regions and other cis regulatory sequences. While during normal development, these patterns are highly regulated, maintained during mitotic cell divisions, and are cell-type specific, they are disturbed in cancer genomes. Indeed, it was shown that a large fraction of enzymes that regulate the epigenome are mutated in many human malignancies (Plass et al. 2013). Importantly, epigenetic modifications are reversible and thus offer the possibility to be reverted by epigenetic therapies. In his presentation ("Cancerepigenetics and the cell-of-origin"), Dr. Christoph Plass highlighted the current concept of epigenetic alterations with a special focus on the cellular origin of the tumor. Recent work in pediatric brain tumors has revised the classification of tumors based on subtypes defined by global DNA methylome analysis. Subgroups are explained by specific DNA methylation patterns originating from the cell-of-origin and maintained in the tumor genome. These subtypes include specific genetic lesions and demonstrate different clinical responses to therapy (Sturm et al. 2012). Chronic lymphocytic leukemia (CLL), on the other hand, is derived from the developmental lineage, in which naive B cells undergo massive epigenetic reprogramming on their way to mature B cells (Oakes et al. 2016). The methylomes of CLL represent this continuum of methylation changes seen in developing B cells. Again, the clinical phenotype correlates closely with the DNA methylome, e.g., CLL subtypes originating from B cells early in B-cell maturations develop into a much more aggressive CLL as compared with those CLLs that develop from cells later in the B-cell maturation cascade. Future goals in this field are now to understanding the molecular basis for epigenetic dysfunction, to develop biomarkers that enable the prediction of response to treatment and to identify synergistically acting drug combinations based on a better mechanistic understanding of the aberrant epigenetic machinery in cancer.

Information about variants and mutations in whole genomes can be obtained today with a little effort thanks to modern sequencing methods. This information is increasingly used to tailor medical treatment to the genetic situation of a single individual, as Dr. Benedikt Brors detailed

in his presentation ("Personalized medicine and genome medicine"). The term "personalized medicine" has been coined for this, but is somehow misleading; it reduces the "person" to its genetic constituents, and with some rights, it has been claimed that all good medical practice has been "personalized" since long before. A more "neutral" term is "precision medicine". The easy availability of information on genetic variants has led to dramatic improvements in several areas of medicine. One of those is treatment of rare diseases, many of which follow Mendelian genetics and are likely to be monogenic. Traditionally, they have been studied by the linkage analysis which requires samples from large families or multiple pedigrees. Now, the genetic causes can be unravelled by a combination of whole-genome or whole-exome sequencing in small families, with the help of information on population frequencies of variants and considering hypotheses about the biochemical pathways that may be involved in pathogenesis (Boycott et al. 2013). About 40–60 % of studied cases can be resolved, which has already frequently resulted in improved therapies. Another area where precision medicine has proven successful is in cancer care. Cancer is almost always caused by somatic mutations in endogenous oncogenes or tumor suppressor genes. Current sequencing methods allow to obtain a comprehensive catalogue of such alterations (Meyerson et al. 2010), which allow for rational choice of targeted therapeutics that interfere with aberrant signalling in cancer cells. According to experience on several hundred cases at the National Center for Tumor Diseases in Heidelberg, improvements can be made in clinical care of advanced solid cancer by improving diagnosis (8 % of cases), and by finding alterations targetable by approved drugs (60 % of cases), which often lead to disease stabilization and improved outcomes. Future research is expected to also expand to the identification of genetic predispositions in individuals and the analysis of complex genetic interactions.

It is a privilege to summarize this symposium in this issue of molecular genetics and genomics. The journal was founded in 1908 and was the world-wide first journal entirely devoted to experimental genetics (Hohmann and Hagemann 2010). Interestingly, it was also the first journal to publish papers in 1908 on non-Mendelian inheritance. It is impressive to see how the field of genetics has maintained its role as a strong component of modern molecular science and how it has evolved over the last 150 years, sparked by the seminal discovery of J. G. Mendel.

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