CRISPR/Cas in crop breeding
Why ethics still matter

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Introduction

CRISPR/Cas1 is one of the newly developed genome editing techniques viewed as revolutionary to crop breeding. It allows a precise modification of genes by adding, cutting or suppressing certain gene sequences of the DNA. Compared to earlier breeding techniques for genetic modification (GM), this system is considered to be easier to apply, more precise, much quicker, and therefore cheaper (Baker 2014). CRISPR/Cas is expected to have great innovative potential in agriculture by speeding up breeding, increasing yields and allowing plant production to occur under less favorable conditions. It has already been successfully applied in the breeding of different agricultural plants such as soybean (Jacobs et al. 2015), maize (Svitashev et al. 2015), tobacco, sorghum, rice (Woo et al. 2015), and tomato (Brooks et al. 2014).

Although CRISPR/Cas generally allows for transgenesis (the transfer of DNA sequences across species), its current application in agricultural biotechnology remains mainly cisgenic (within species boundaries). CRISPR/Cas-based cisgenesis allows for creating new products that could in principle also be the outcomes of natural evolution or conventional breeding techniques. It also offers the possibility of "reverse breeding", that is the re-introduction of properties that were lost in the course of breeding (Palmgren et al. 2015). When using common tests the genetic modification of DNA could not be traced in the new products up to now (Ahmed 2002; Araki and Ishii 2015). Thus, the cisgenic products cannot be identified as genetically modified organisms (GMOs). Nucleotides (DNA and RNA) can be synthesized so that they are molecular equivalent to the native temples. Therefore, they are so-called nature-identical GMOs.2

These new options for breeding have shifted the societal debate on genetic engineering in a new direction, opening a variety of controversies. One of these is whether cisgenic plants should be viewed as genetically modified at all, considering that cisgenic plants can be entirely indistinguishable from plants that are the outcomes of traditional breeding techniques. The answer that is given to this question has implications regarding the nature of the regulations that may be applied to these products, and even the need for applying regulation of any kind. This, in turn, may significantly influence the profitability of the innovation. A second controversy concerns the permissibility of reverse breeding techniques in organic farming. Within both debates, the concept of naturalness plays a key role and is used as an argument both by proponents and opponents of CRISPR/Cas.

Against this background, the aim of this chapter is threefold. First, reconstruct the societal debate on the application of CRISPR/Cas and its regulation; second, analyze the different understandings of naturalness that lead to different judgments about the moral acceptability of the technology; and third, argue that natural identity is not a sufficient argument to reject all ethical concerns that can be moved to CRSIPS/Cas.

Reconstruction of the societal debate

A key point within the debate on the use of CRISPR/Cas in plant breeding is whether cisgenic plants should be viewed as GMOs or not. Current EU Law defines GMOs "an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination" (European Parliament 2001, 4).

EU jurisprudence on GMOs was developed at a time when GMOs meant introducing transgenic DNA into a genome. Thus, the regulation does not distinguish between transgenic and cisgenic plants, and defines GMOs by looking at the process of creation and not its outcomes. If a technique is defined as GM, it has to undergo a special risk assessment that substantially increases the cost and time needed for approval. At the same time, EU law allows for exceptions from this procedure in cases of mutagenesis and cell fusion (European Parliament 2001, 5, 18). If cisgenic plants are viewed as GMOs, then the advantage of rapid breeding success can be neutralized by the time that is needed for the approval procedure. This has negative consequences for the profitability of the innovation. Furthermore, products under EU regulation have to be labelled as GMOs, which might have a negative consequence for consumer acceptance. Thus, the categorization of CRISPR/Cas as a genetic modification is both a societal question of risk management and an economic question of profitability for breeding companies.

Unsurprisingly, the leading breeding companies call for a product-oriented regulation that would not define cisgenic plants as GMOs. Their key argument relies on the natural identity of the modified and traditional plant (KWS 2017). This argument has also been made by scientists (Araki and Ishii 2015; Huang et al. 2016; Schouten, Krens, and Jacobsen 2006), and it holds that cisgenic plants obtained through CRISPS/Cas techniques are to be assimilated to traditionally bred plants because the transferred genes originate from the same gene pool. According to this argument, no changes in fitness occur that could not also occur through either traditional breeding techniques or natural gene flow. Hence, cisgenesis carries no distinctive risks (e.g. regarding potential effects on non-target organisms or soil ecosystems, toxicity or possible allergy risks emanating from GM food or feed) other than those that are also incurred with traditional breeding techniques. Therefore, leading breeding companies call for an approval procedure of CRISPS/Cas products like that used for products of traditional breeding (Carroll et al. 2016; Huang et al. 2016).

In contrast, critics argue that although the product might be identical to those developed by nature, the process is highly artificial. All GM techniques directly interfere at the level of the genome by inserting material that was produced outside the cells. This degree of intrusion into the cell is viewed as a risk because the consequences for the plant are not sufficiently known. Critical biologists, such as Then (2016) and Steinbrecher (2015), argue that CRISPR/Cas is indeed more precise than other GM techniques, but that it is still not free of errors. They note that off-target effects might occur because of insufficient specificity of the nuclease, which causes the DNA to be cut in several regions of the genome instead of the one intended. Therefore, critics call for a regulation of the process, as is currently the case under the EU regulation, to guarantee the traceability of the genetic modification and to protect consumers' right to know which food products are produced from genome-edited plants. From the critics' perspective, the safety of the technique cannot be guaranteed reliably, and therefore a regulation of the modification process is urgently needed.

Similar divergences become apparent in the discussion about the acceptability of CRISPR/Cas for organic breeding. Organic farmers have different breeding objectives than regular farmers because of their general rejection of synthetic fertilizer and pesticides. Therefore, they need cultivars adapted to low-input growing conditions, with a high resistance to pest and disease (Nuijten, Messmer and Lammerts van Bueren 2017).

The introduction of genes from older varieties that are thus adapted and resistant offers a possibility to better satisfy the specific requirements of organic farming. The application of the CRISPR/Cas technique in breeding would speed up their breeding successes tremendously. Yet when Urs Niggli, head of the Swiss Research Institute of Organic agriculture "Fibl" (Forschungsinstitut für biologischen Landbau), proposed CRISPR/Cas as a possible option in organic breeding (Maurin 2016), the majority of members of the organic farmers' association distanced themselves from his position (Bio Suisse 2016; Bioland 2016). For them, the CRISPR/Cas technique is a genetic modification and therefore not compatible with the principles of organic breeding and farming. Therefore, IFOAM EU, part of the International Federation of Organic Agricultural Movements, calls for additional risk assessment, and for labelling CRISPS/Cas products under GMO regulation in order to distinguish non-GM production and increase transparency and freedom of choice for farmers and consumers (IFOAM 2015).

In the scientific literature, there are opposing positions regarding the compatibility of organic farming with new breeding techniques such as CRISPS/ Cas. Generally, organic farming interprets agriculture as a process that includes agro-ecological, socioeconomic, and ethical principles. IFOAM has defined four core principles to reflect this holistic understanding of agriculture: health, ecology, fairness and care (IFOAM 2014). Opponents of CRISPR/Cas have argued that this new way of breeding conflicts with the principle of health, if that principle is understood as supporting the wholeness and integrity of living systems. From this biocentric perspective, any alteration of DNA violates the integrity of the genome as part of a living entity (Nuijten et al. 2016; van Bueren et al. 2003). In contrast to this, proponents note that reverse breeding can reduce the need for chemicals and is therefore not only compatible with organic farming but also urgently needed. It promotes the health of the plant, and is therefore compatible with the principle of health: thanks to it the plant can better cope with adverse environmental conditions. Here, reverse breeding is viewed as a return to nature rather than a further departure from it (Andersen et al. 2015; Palmgren et al. 2015).

Breeding between biomimicry and biofact

Different opinions about the need and acceptability of human interference with nature can lead to opposing positions regarding the treatment of CRISPR/Cas modified plants. It must be remembered that breeding is by definition human interference with natural processes, as the ultimate aim of breeding is to change plants to suit human needs. Humans have done this since the Neolithic. At the same time breeding, and agricultural production more generally, are not entirely artificial, as they also crucially depend on natural systems at the molecular as well as higher levels. No clear-cut boundaries between nature and technology seem to exist in agriculture. Our explorations of nature up to the molecular level, and decoding and modifying of natural processes, are further blurring the distinction.

At first glance, the current public debate focuses on the legal question of regulation and labeling. But when looking at the arguments of both proponents and opponents of process-targeted regulation, the question of nature or naturalness is clearly central. In this context, the notion of naturalness is used not only for describing different degrees of human interference with plants but also as a moral category (Van Haperen, Gremmen and Jacobs 2012). However, the classification of processes as “natural” or “unnatural” is notoriously ambiguous, and this is in evidence in the opposing positions that those calling for or rejecting the regulation of cisgenic crops take.

The two groups seem to employ different understandings of naturalness. In her article “Dimensions of Naturalness”, Siipi (2008) classifies the different understandings of naturalness or unnaturalness at play in public and scientific debates in bioethics. These categories are helpful to understand how it can be possible to argue both for and against applying CRISPR/Cas by invoking naturalness.

The two understandings of naturalness that are important for the CRISPR/Cas debate are what Siipi (2008) calls history-based and property-based naturalness. While history-based naturalness emphasizes the origin of an entity, or the kind of modification it has gone through, property-based naturalness looks at the current properties of an entity disregarding the manner in which they appeared. For history-based naturalness, the occurrence of human involvement is the criterion for judging an entity as natural or unnatural (human interference itself is viewed as unnatural). On some views, an entity can only be either natural or unnatural. On other views, different degrees of naturalness are possible depending on the qualities of the human interference, such as intensity or duration. Property-based naturalness, on the other hand, ignores processes and judged naturalness by comparison with models.

With regard to CRISPR/Cas, a “historically natural entity”, that is a wild plant with its original molecular composition, is used as the reference model.3 Proponents of CRISPR/Cas typically have a property-based understanding of naturalness. By indicating that the molecular structure of synthesized genes can be identical with that of natural genes, and by arguing that reverse breeding leads to a back-to-nature crop (Palmgren et al. 2015), they clearly interpret naturalness as property-based similarity to wild entities employed as reference models. Hence new breeds that exhibit similar properties as the wild ones are viewed as natural. The more similarities exist between a new crop and wild historic plants, the more natural the new crop is. Furthermore, CRSIPR/Cas can be viewed as natural because the process of gene transfer in the lab is similar to a biological mechanism (Belhaj et al. 2015). Genome editing via CRISPR/Cas applied by the plant breeder is also, at the same time, a mechanism naturally occurring in bacterial cells: the CRISPR sequences provide bacteria with an immune defense against viral attacks by introducing foreign viral gene sequences into a bacterial DNA (Belhaj et al. 2015). On this showing, CRISPR/Cas is a discovery of a natural mechanism, and as a new breeding technique, it is only mimicking nature.

Understanding new breeding technologies as biomimicry is typical of what Zwart (2009) calls a “techno-science perspective on nature” where nature is viewed as a great source of products and processes and as an inspiring source of knowledge to be discovered, explored and imitated. Nature provides the scientist with the tools and techniques he or she can use to develop new products and procedures to solve human problems (Blok and Gremmen 2016), optimize natural processes to human needs and finally “[…] design the ideal plant type” (Koornneef and Stam 2001, 159).

Categorizing a product or a process as natural serves at the same time as a moral relief: according to this property-based understanding of naturalness, no moral concerns arise as long as the new product could at least theoretically come into existence without human interference (Weigel 2017). From this perspective, the product is morally acceptable because it is natural.

Opponents of CRISPR/Cas, on the other hand, typically have a history-based view of naturalness, and focus on the process of human interference with nature and not just (the properties of) its outcomes. On this view, plants modified by CRISPR/Cas techniques are more unnatural than traditionally bred plants because CRISPR/Cas plants have undergone greater human-caused changes than traditionally-bred plants. This is true even if the genotype of the plants is similar. Here, it is the processes as such that raise moral concerns. The demand to regulate cisgenic modified plants under EU GM schemes shows that the key concern is not the transition of species boundaries and the unnaturalness of the outcome, but the unnaturalness of the process of human interference with the cell. On this view, although CRISPR/Cas may in principle occur naturally, the fact that it is now carried out by humans raises moral concerns. This is part of a general criticism of technologies that infringe on natural processes.

Opponents of CRISPR/Cas view these new plants as one step closer to "biofacts" (Karafyllis 2003), where more and more key aspects of nature and naturalness are lost. The term biofact expresses the concern that nature is no longer the non-human – in the Aristotelean understanding of that which just comes into being – but is now shaped and designed by technology and thus becomes an artificially created entity (Aristotle 1980). For opponents of CRISPS/Cas, the fundamental question still lingers of whether the acquisition of natural processes for human purpose is legitimate at all. Molecular biology allows what Lee (2003) calls an ontological transformation of living organisms from natural beings into "biotic artefacts". Nature changes from something that grows and develops to something that is made (Dabrock 2009). For those who oppose it, this technology is not a step closer to more naturalness but a step closer to achieving control of nature and its processes. On these views, the use of CRISPS/Cas remains a highly controversial and urgent moral question.

Conclusions

The natural identity of CRISPS/Cas-modified plants and conventionally bred plants is an observed empirical fact. The molecular composition of the plants can be the same. Proponents of a deregulated application of CRISPR/Cas argue that because of this natural identity "there is no scientific or other logical reason to single out the "process" of the genome editing for onerous regulation" (Carroll et al. 2016, 479). However, the conclusion connecting the empirical evidence of natural identity to calls for a certain kind of regulation and risk management (or omission thereof) seems based also on unspoken value-judgments that may be well disputed in the context of societal debate. What has become apparent above while specifying the various meanings of "natural" or "naturalness" is that the term itself is ambiguous and thus open to interpretation.

Comparing conventionally bred plants with genetically modified plants on the basis of their molecular composition, and concluding that molecular equivalence leads to equivalent risks, is only one way of deciding of the acceptability of these new technologies. In contrast, one might compare plants on the basis of their phenotypes, or their interactions with the environment in a more holistic vein; or one might raise general deontological objections against the disturbance of the genome – as the debate on the application of CRISPR/Cas in organic farming shows. Thus, differences in the acceptance of the new technology are not solely caused by a lack of knowledge or irrationality of lay consumers and citizens, as often suggested by “techno-science” enthusiasts, but are traceable to different value-judgments about the extent to and the ways in which humans should interfere, and be allowed to interfere, with nature. Concluding from natural identity that the risk of the new technology is generally acceptable is to take a moral stance, not to enunciate a matter of fact. Natural scientists in biotechnology need to be aware that ethics is intrinsic, not extrinsic to their task (Bruce 2002). That means that the broader public has to be not only informed about, but also involved in, decision-making on new technological developments such as CRISPS/Cas. A societal discourse on the guiding values regarding the development and application of any new technology should be an integral part of natural science, beginning in the research design phase.

Notes

1.Clustered regulatory interspaced short palindromic repeats, Cas is a CRISPR-associated protein.

2.Kim and Kim (2016) question this assumption by presenting some cases where cells transfected with CAS9 and guide RNA did contain small insertions of foreign DNA at off-target sides.

3.Siipi (2008) further identifies “normality”, understood as a statistical or functional concept, and “human nature”, as two other possible reference models.

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