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Rice Epigenetic Pathways: Great Genetic Variation and Implication for Rapid Rice Breeding

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Abstract

Rice, as one of the most important crops in the world, is facing an ever-accelerating challenge from climate change. Epigenetic modification with its substantially high epimutation rate and the possibility for some epigenetic variation to act as a heritable contributor to crop environmental adaptability may hold great potentials for rapid crop breeding. Epigenetic modification is controlled by epigenetic pathways, and mutations disturbing the epigenetic pathways may lead to significant epigenetic and/or genetic changes. This is especially true for rice, whose genome is rich in epigenetic modifications and transposable elements (TEs) that are generally epigenetically silenced. Here, in this paper, we first reviewed the pathways that establish, maintain and remove rice DNA methylation, which is the most well studied epigenetic marker, as well as the genes that are involved. We then discussed how TEs amplify the phenotypic impact of epigenetic changes that could be a result of epigenetic pathway disturbances. At last, we presented the enormous amount of rice genome data that are publically available, within which great genetic variation in the genes that are involved within the epigenetic pathways is embedded. This genetic variation awaits to be exploited for their potentials in generating a heritable source of variation for rapid environmental adaptation, which may hold tremendous importance for rice breeding in the face of climate change.

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Introduction

As one of the most important food crops in the world [1,2], rice (*Oryza*) is, unfortunately, rather sensitive to climate change, for its yield may be significantly reduced by increasing temperature, by rising sea levels (and the associated salinity intrusion), as well as by flooding and droughts [3]. Genetic studies have been making great efforts to improve rice ability to handle environmental stresses [3,4]. However, there are still lots to be done, especially when the ever-accelerating climate change is bringing more and more unpredictable and extreme weather.

Epigenetics, the study of chromatin marks that include DNA methylation and histone modification [5], may provide great potentials for crop breeding in a rapidly changing climate, due to the remarkably high epimutation rate [6] and the possibility for some epigenetic variation to be a heritable contributor to crop environmental adaptation [7-9]. Epigenetic modifications exist ubiquitously in nature, they can regulate gene expression by controlling the accessibility of DNA to transcription machinery, and are therefore vital not only for multicellular organisms' development [10-12], but also for all life's response to their living environment [2,13,14]. Comparing to genetic mutation, epigenetic mutation has been found to occur at a much higher rate (can be orders of magnitude more frequent) [6,15,16], especially under stressful conditions [7,17,18]. Many spontaneous or stress-induced epigenetic changes can be heritable across generations [7,19-22] and some of these heritable epigenetic changes occur in or near genes that are involved in stress-responsive pathways and therefore may help crop handle adverse environmental conditions by assisting the regulation of these stress-responsive genes' expression [7,8,22].

Epigenetic modification is generated through epigenetic pathways, during which epigenetic modifications get established, maintained and removed [5,14]. Therefore, mutations at genes encoding enzymes that are involved in epigenetic pathways will have a good chance to create a genome-wide impact on an organism's epigenetic profile [23-26]. This impact on epigenetic profile may hold great potential to provide an organism with a heritable source of variation for rapid environmental adaptation. Rice is one of the best crops so far that can be used for exploiting genetic variation within the epigenetic pathways to help improve breeding in the face of climate change for the following reasons: 1) the rice genome is significantly rich in transposable elements (TEs), which can help amplify the phenotypic impact of epigenetic changes [27]; 2) rice is the most well studied cereal crop within genomics and epigenetics so far [2], so that the rice epigenetic machinery has been relatively well investigated [5], and 3) there are plenty of rice genome data (>3000) that are publicly available and that can serve as a rich source of genetic variation for exploitation [1,28].

DNA Methylation Pathways in Rice with many involved Genes having been Identified

The epigenetic state of an organism is the outcome of different molecular mechanisms such as DNA methylation, histone modifications and variants, as well as non-coding RNA changes [2,14,26,29]. Among these molecular mechanisms, DNA methylation at the 5' position of cytosine has been most well studied so far especially from the perspective of inheritance mechanism and variation [14,30,31]. DNA methylation is established, maintained and removed by a series of pathways [14], and most of the proteins that are involved in these pathways have already been identified for rice [5], which provides a good starting point for exploiting the breeding potential of rice's epigenetic pathways. The recent progress about DNA methylation pathways in rice has been reviewed by Deng et al. 2016 [29] and Lanciano & Mirouze 2017 [5], therefore here we will only give a brief summary of it.

Epigenetic pathways are relatively conserved between different plant species [2]. As in *Arabidopsis thaliana* [14], rice de novo establishment of DNA methylation is carried out by the RNA-directed DNA methylation (RdDM) pathway [5]. There is also RdDM in animals though with a much less important role [32,33]. During RdDM, small interfering RNAs (siRNA) are first produced, via several steps, from the target locus, and they then, with the help of a set of proteins, head to the target locus, where the target locus gets eventually methylated by an enzyme that is called domain rearranged methyltransferase (DRM) [5,14]. There are three DRM-encoding genes that have been identified in rice so far, *OsDRM2*, *OsDRM1a* and *OsDRM1b*, with the last two not being expressed [34]. RdDM takes on two different forms in plant: canonical and non-canonical. The main difference between these two forms lies in the production of siRNA. Canonical RdDM is a proactive de novo methylation process, during which siRNAs production starts from the transcription of target locus by RNA polymerase IV (POL IV) [5,14]. In contrast, the non-canonical RdDM is a rather passive remedial strategy that takes action when regular transcription of the target locus (by POL II) has already occurred, and it is the mRNAs produced via regular transcription that will be processed into siRNA [14,35,36]. Apart from OsDRM2, POL IV and POL II that have been mentioned above, there are a bunch of other proteins that have also been identified to be possibly involved within the rice RdDM pathways: OsRDR1, OsRDR2, OsRDR6, OsDCL3a, OsDCL3b, OsAGO4a, OsAGO4b, OsAGO1a, OsAGO1b, OsAGO1c, OsAGO1d, OseIF4A, POL V, WAF1 and OsDCL4 etc. [5].

Different from animals where DNA methylation mainly occurs at the CG dinucleotide sequence context, plant DNA methylation takes place at three different sequence contexts: CG, CHG and CHH (H = A, T or C) [37]. Plant DNA methylation can be maintained by different mechanisms depending on the sequence context [14]. In rice, CG methylation is mainly maintained by the methyltransferase OsMET1-2, that is a possible ortholog of the mammalian DNMT1 enzyme [5]. DNMT1 recognizes hemi-methylated CG during DNA duplication and methylates the unmethylated cytosine in the newly-synthesized daughter DNA strand [38]. Apart from OsMET1-2, another methyltransferase, OsMET1-1, has also been identified in rice, and OsMET1-1 may have a minor and/or redundant role in maintaining the CG methylation [5]. The maintenance of rice CHG methylation is mostly the responsibility of the plant specific chromomethyltransferase OsCMT3a [5]. Another rice chromomethyltransferase, OsCMT3b, is also involved in CHG methylation but with a much smaller role. A third rice chromomethyltransferase (OsCMT2) has also been identified, however the function of OsCMT2 is still unknown [5]. Rice CHH methylation is mainly maintained by OsDRM2 [39] that is also involved in the RdDM pathways [40]. The *A. thaliana* ortholog of OsDRM2, DRM2, maintains CHH methylation through RdDM at RdDM target regions that include certain transposons and repeat sequences [14]. In addition, two rice chromatic remodeling proteins OsDDM1a and OsDDM1b also play roles in maintaining DNA methylation; OsDDM1a/b act at CG and CHG methylation within both euchromatins and heterochromatins, but at CHH methylation of small TEs that are mainly located in euchromatins [39].

DNA methylation could be passively lost due to failure in maintaining it, it could also be actively removed enzymatically [14]. Different from DNA methylation reaction that is catalyzed by one single enzyme, active DNA demethylation reaction needs a group of enzymes to catalyze several steps of the reaction: DNA glycosylase, apurinic/apyrimidinic endonuclease, DNA phosphatase and DNA ligase etc., with the first enzyme, glycosylase, being conventionally referred to as DNA demethylase [14]. So far, there has been six DNA glycosylases that have been identified in rice: ROS1a, ROS1b, ROS1c, ROS1d, DML3a, and DML3b, with ROS1a being most expressed. In addition, the loss-of-function mutation of ROS1a leads to serious developmental problems [5,29].

The Abundant TEs within the Rice Genome Amplify the "Voice" of DNA Methylation Pathway Disruption

Comparing to *A. thaliana*, the consequences of DNA methylation pathway disruptions in rice tend to be more serious [5,27,29]. For example, functional disruption of *OsDRM2* leads to failure of RdDM, resulting in various developmental problems such as complete sterility [34,39], while the loss-of-function mutation of the orthologous gene *DRM2* in *A. thaliana* showed almost no morphological differences from the wild type [41]. This different "behavior" of rice from *A. thaliana* may be due to the much higher levels of DNA methylation and the greater proportion of transposable elements (TEs; generally epigenetically silenced [27,42]) in the rice genome [2,27,29,43], as well as the fact that most rice genes have associated TEs [27]. For example more than 85% of the African cultivated rice genes have been found to be associated with TEs [44].

Epigenetic modification can regulate gene expression and is therefore able to influence phenotypes [2,14], while the substantial TEs in rice genome act like a "loudspeaker" to amplify the phenotypic impact of epigenetic changes that could be a result of epigenetic pathway disruptions. This is, firstly, because TEs are the major targets of de novo RdDM pathways [33], which may process beyond the targeted TEs and methylate the flanking sequences [42,45,46]. The spreading of DNA methylation from gene-associated TEs to gene body and/or regulatory sequences may help regulate the expression of the involved genes [42,47]. For example, it has been shown that reducing the expression of the *OsDCL3a* gene that is involved in RdDM can cause ectopic expression of hundreds of MITE-related genes (MITE is one kind of TEs) in rice [27,48]. Therefore, it has been proposed that epigenetic regulation of genes may be originally evolved for silencing invading TEs and virus [42].

Secondly, in rice, under stressful condition, TEs may be released from their epigenetic controls as a result of stress-induced epigenetic changes and become activated [27,49]. This process may be facilitated by certain mutations within, or other disruptions of the epigenetic pathways [14,50]. For example, an *A. thaliana* mutant impairing the POL IV enzyme that is important for RdDM showed boosted transposition of one specific TE (*ONSEN*) in response to heat stress, comparing to the wild-type plant [50]. In rice, overexpression of the *ROS1c/DNG701* gene that is involved in DNA demethylation caused more frequent transposition of one specific TE (*Tos17*) in calli (a stress-like condition) [51]. The activated TEs transpose from one genomic region to another and this will not only modify genomic sequences and generate genetic diversity [27,49], but also likely bring epigenetic modification to the recipient genomic regions that may establish new TE-associated genes [50].

These TE-induced epigenetic and genetic variation may hold great potentials for creating phenotypic diversity that would contribute to rice environmental adaptability [27]. For example, an artificially induced insertion of one specific TE (*mping*) into the intron of the rice *Hd1* gene, which is important for photoperiod sensitivity, has been shown to cause flowering time change, and this may help Nipponbare adapt to different photoperiods; Nipponbare is the temperate *japonica* rice cultivar that flowers under longer day length than the tropical *japonica* rice cultivars [27,52].

Over 3000 Rice Genomes as a Rich Resource of Genetic Variation Awaits to be Exploited

From above, we know that disturbance of epigenetic pathways may create both epigenetic and genetic variation, which could modify phenotypes and might therefore help breed for climate changes. Then, where are we going to find genetic variation that can cause such epigenetic pathway disturbance? For the economically very important crop, rice, there is, luckily, a large amount of publically available genome data that we can resort to.

Rice has the smallest genome (ca. 375 mega base pairs [1]) among the major cereal crops [52], therefore its genome has been extensively sequenced [44,53-55]. Especially, the 3000 Rice Genomes Project has acquired the sequences of 3010 Asian cultivated rice (*Oryza sativa* L) genomes with a global representation of the genetic diversity within this rice species [1,55]. Rice is well known for its substantial genetic diversity [56-61], for example, a recent analysis of the 3010 rice genomes has revealed 29 million single nucleotide polymorphisms and over 2.4 million indels [1]. This enormous amount of genetic variation within the over 3000 rice genomes represents a great starting point for exploring the genes encoding proteins that are involved within the rice DNA methylation pathways in their potentials to influence epigenetic profiles.

Conclusion and Future Perspective

In the agriculturally very important crop, rice, whose genome is rich in epigenetic modifications and TEs [2,27,29,43], epigenetic pathways disturbance may dramatically change the epigenetic profile, and could therefore lead to phenotypic variation [5,27,29]. The phenotypic impact of epigenetic changes in rice may be significantly amplified by TEs via creating both epigenetic and genetic variation [27,42,45,46,49]. Now many genes involved in the pathways of establishing, maintaining and removing DNA methylation, which is the most well studied epigenetic marker so far, have been identified [2,5]. The genetic variation of these genes that are embedded within the over 3000 publically available rice genomes [55] awaits to be exploited in their potential to generate a heritable source of variation for the rapid adaptation of rice, which may hold tremendous importance for rice breeding that is facing an increasing challenge from climate change.

Considering the likely large amount of genetic variation at genes that are embedded within the over 3000 rice genomes, it would be time- and labor-consuming to experimentally examine each of the genetic variants. Therefore, a preliminary selection by, for example, predicting the possible influences of these genetic variants on the function, activity, stability, etc., of the involved proteins would be a smart starting point.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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