Review of: "Improving disease resistance in plants by editing the epigenome"

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In this work, Veley et al., used a very smart, elegant and nice strategy to tackle the problem of remove or alter an S locus, which can have negative effects, to gain resistance. Their rationality was, no to modify the sequence of the locus, but to alter their methylation status. The S locus is a region targeted by a TAL effector (TAL20 from Xpm), which specifically bind to the promoter of the cassava MeSWEET10a gene, and induce their expression. To achieve this goal, the authors created a ZincFinger (ZF) targeting the EBE recognised by TAL20 in the promoter of the cassava MeSWEET10a gene and fused it to the DMS3 gene coding for one of the proteins of the RNA-directed DNA methylation (RdDM) pathway. In a first experiment the authors, using EMSA, demonstrated the TAL is unable to bind to the methylated version of the corresponding EBE. After that they created transgenic cassava plants containing the ZF alone or fused to the DMS3, showing a specific methylation only in the second group of plants and specifically in the TAL binding region. This methylation was correlated with a suppression of the MeSWEET10a gene induction after Xpm infection and reduction in symptoms. Although the rationality and experiments are well supported and conducted, from my point of view there are several points should be considered and explained:

1. The main advantage of this approach is that it not involves the modification of a gene, which is necessary for normal growth and reproductive development of the plant. However I wonder if the methylation status is stable. In this case it will cause the same problems. Even if the gene sequence is not modified, the expression is impaired by the methylation, and the gene will not be functional for the normal process of the plant. This aspect should be discussed in the manuscript.
2. The authors evaluated only the methylation status and expression on leaves. What happen in other tissues, or during the development of the plant? Is this status transmitted to other generations?
3. My main concern is the use of to cassava varieties for the experiments. The control plants are transgenic containing the ZF alone, that are derived from the 60444 variety. On the other hand, the ZF fused to the DMS3 were only generated for the TME419 variety. These are two varieties belonging to different genetic background, which can mask the results. In this case the experiment should be cleaner and be conducted using the same variety.
4. Another good control to be included is the generation of a ZF targeting other genomic region fused to DMS3.
5. The authors evaluated the visual symptoms of the plants, but to give robustness to the experiments should include bacterial growth and/or AUDPC.
6. Could the authors include more information of the RNA-directed DNA methylation (RdDM) pathway in the introduction and establish if, for example, it includes the siRNA production.
7. According to 6 point, it will be nice if the authors could demonstrate the presence of specific siRNAs.

8. Finally, the authors should include the new taxonomic name for Xanthomonas axonopodis pv. manihotis, which is now Xanthomonas phaseoli pv. manihotis.