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REVIEW

Plant tissue culture environment as a switch-key of (epi)genetic changes

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Abstract

The in vitro tissue cultures are, beyond all difficulties, an essential tool in basic research as well as in commercial applications. Numerous works devoted to plant tissue cultures proved how important this part of the plant science is. Despite half a century of research on the issue of obtaining plants in in vitro cultures, many aspects remain unknown. The path associated with the reprogramming of explants in the fully functioning regenerants includes a series of processes that may result in the appearance of morphological, physiological, biochemical or, finally, genetic and epigenetic changes. All these changes occurring at the tissue culture stage and appearing in regenerants as tissue culture-induced variation and then inherited by generative progeny as somaclonal variation may be the result of oxidative stress, which works at the step of explant preparation, and in tissue culture as a result of nutrient components and environmental factors. In this review, we describe the current status of understanding the genetic and epigenetic changes that occur during tissue culture.

Key message

Variation appeared in regenerated plants as well as variation inherited by generative progeny of regenerants can may many, positive or negative impact, of gained plant materials. This review focused on factors that triggered this phenomenon with underlying oxidative stress.

Keywords Somaclonal variation · Oxidative stress · Epigenetic · Methylation

Introduction

Plant tissue cultures (PTC) play a crucial role in modern biotechnology. They are extensively used in studies on plant developmental processes (Firn et al. 1994), gene functioning (Deng et al. 2010), micropropagation (Kumar and Redd 2011) and generation of transgenic plants with specific industrial and agronomical traits (Loyola-Vargas and Ochoa-Alejo 2018). Therefore, PTC may impact in crop improvement and plant breeding by elimination of viruses for healthy plant material (Perotto et al. 2009; Taşkın et al. 2013), by preservation of germplasm of vegetatively propagated plant crops (Rajasekharan and Sahijram 2015) and by threatened or endangered plant species rescue (Sarasan et al. 2006). The plant in vitro cultures are of interest for the production of secondary metabolites of commercial interest (Loyola-Vargas and Ochoa-Alejo 2018). Plants obtained via PTC were used in genetic studies to generate mapping population for dissection of QTLs linked to agronomic traits (Tyrka et al. 2018) and in studies of mobile elements (Shingote et al. 2019). For a long time, in vitro culture methods were considered as the way of generating plants that are identical to the donor plants (Metakovsky et al. 1987). They were also used to obtain genetically uniform materials, e.g., for breeding purposes (Weyen 2009). However, even earlier studies (Heinz 1973; Larkin and Scowcroft 1981) demonstrated that in vitro tissue cultures are prone to mutations (Kaeppler et al. 1998) and many phenotypic changes were described (Zhang et al. 2014). With the development of modern techniques, it became evident that PTC are also affected by epigenetic changes exhibited at, e.g. histone methylation/demethylation (Grafi et al. 2007), DNA methylation levels (Han et al. 2018), changes in gene expression

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(Kabita et al. 2019) and involve a wide range of small RNAs (Li et al. 2012). Numerous such examples were published in the literature (Jiang et al. 2011; Miyao et al. 2011; Neelakandan and Wang 2012; Sabot et al. 2011). However, the mechanisms explaining the somaclonal variation phenomenon are still to be assessed. Nevertheless, some steps seem to be foreseen. Firstly, stressful environment (tissue cultures itself) is the inductor that affects the cell membrane and wall; then some signals are transmitted to organelles resulting in reactive oxygen species (ROS) (Wachsman 1997) possibly via changed balance in biochemical pathways (Kumaravel et al. 2017). The change is transmitted to the nucleus via signaling (retrograde) pathway (Apel and Hirt 2004; Chi et al. 2015) inducing (epi)genetic reaction that leads towards cell dedifferentiation and differentiation. The later processes involve histone modification (Grafi 2004), DNA methylation changes (Ikeuchi et al. 2015; Lee and Seo 2018), and alterations in gene expression (Wibowo et al. 2018). As soon as the new balance is established, the signal is transmitted back to the chloroplasts and mitochondria (anterograde). In the given review, the state of knowledge concerning the induction of tissue culture induced variation will be discussed.

Tissue cultures as a stressful environment

Stressful environments (Benderradji et al. 2012; Grafi and Barak 2015; Leljak-Levanić et al. 2004) are known to play a pivotal role in plant regeneration via tissue cultures (Fortes and Gallusci 2017; Hirsch et al. 2012; Liu et al. 2015). Cold and osmotic stresses applied in darkness are the most common once used to regenerate plants (Sood and Dwivedi 2015). Such conditions induce oxidative stress that leads towards the production of pro-oxidants or ROS (Wachsman 1997).

Firstly, stress is sensed by the plasma membrane and cell wall (Das and Roychoudhury 2014). In the membrane, the NADPH-dependent-oxidases are the enzymes that respond to stress (Apel and Hirt 2004; Kwak et al. 2003) producing $O_2^{\cdot-}$, which may spontaneously convert to H_2O_2. The cell wall, generates $OH^{\cdot}$, $O_2^{\cdot-}$, H_2O_2, and $^1O_2$ with the help of diamine oxidases that utilize diamines or polyamines.

Stresses accompanying tissue culture plant regeneration (Nivas and de Souza 2014), affect the proper functioning of the chloroplast, mitochondria, peroxisomes, and apoplasts (Roychoudhury et al. 2008); however, endoplasmic reticulum, cell membrane, cell wall, and the apoplasts functions are also disturbed (Das and Roychoudhury 2014) resulting in ROS. Under normal conditions, ROS are removed via antioxidants (Foyer and Noctor 2005), but under stresses, their production and elimination are not in balance (Karuppanapandian et al. 2011; Krishna et al. 2016; Wachsman 1997). Free radicals like $O_2^{\cdot-}$, $OH^{\cdot}$ and non-radicals like H_2O_2 and $^1O_2$ are the leading players controlling growth, development in plants, and response to environmental stimuli. Under stress like cold, heavy metals, used in tissue cultures cellular homeostasis is not preserved, and the excess of ROS may manifest in the degradation of pigments, proteins, lipids and DNA affecting cellular functioning (Das and Roychoudhury 2014) than inducing tissue culture variation.

Chloroplasts and peroxisomes are the primary sources of ROS under light conditions, while in the dark the mitochondria is the source of ROS (Choudhury et al. 2013). In chloroplasts the photosystems, PSI and PSII are the key sources of ROS production. Abiotic conditions (e.g., water stress and limited CO_2 concentration), in the excess of light induces the formation of $O_2^{\cdot-}$ at the PSII (the Mehler reaction). The PSI converts $O_2^{\cdot-}$ into H_2O_2 ending with $OH^{\cdot}$ radicals (Miller et al. 2010). PSII is also involved in the production of $^1O_2$. This element can initiate growth inhibition in plants (EXECUTOR1 and EXECUTOR2 programs) (Lee et al. 2007).

The peroxisomes are also the source of H_2O_2 due to their integral oxidative metabolism (Palma et al. 2009). They also produce $O_2^{\cdot-}$, during the various metabolic processes.

Mitochondria also generate H_2O_2 and $O_2^{\cdot-}$ (Navrot et al. 2007), though on a smaller scale. Plant mitochondria produce O_2 and carbohydrate-rich environment (Rhoads et al. 2006) and are involved in photorespiration. The mitochondrial electron transfer chain (mtETC) encompassing Complex I and III (Møller et al. 2007; Noctor et al. 2002) reduces O_2 to form the ROS. The NADH Dehydrogenase or Complex I reduces O_2 to $O_2^{\cdot-}$ in its flavoprotein region. The reverse electron flow from Complex III to I is enhanced due to lack of NAD^+-linked substrates favoring leakage of electrons to O_2 generating $O_2^{\cdot-}$ (Murphy Michael 2009). The $O_2^{\cdot-}$ is converted to H_2O_2 (Sharma et al. 2012). Mitochondria produces ROS during normal conditions, but is boosted at abiotic stress conditions (Pastore et al. 2007) affecting the tight coupling of ETC and ATP synthesis, resulting in over reduction of electron carriers pool, generating ROS (Blokhina and Fagerstedt 2010; Rhoads et al. 2006) regulated by antioxidant machinery (Das and Roychoudhury 2014).

ROS can affect the exchange of signals between chloroplasts or mitochondria with the nucleus, namely retrograde or anterograde signaling (Suzuki et al. 2012). As the result of retro- and anterograde chromosome number changes (from polyploidy to aneuploidy), chromosome strand breakage, rearrangements, and DNA base deletions and substitutions (Czene and Harms-Ringdahl 1995) may appear. The changes are ruled by epigenetic mechanisms affecting the whole (epi)genetic network influencing the in vitro tissue culture induced variation (Kaeppler et al. 2000). Growing number of studies make a shift from genetic towards epigenetic mechanisms influencing tissue culture induced or somaclonal variation (Rodriguez-Enriquez et al. 2011).

Epigenetic aspects of plant regeneration via in vitro tissue cultures

It is well recognized that differentiated plant cells do not lose their developmental potentialities but retain plasticity to dedifferentiate and acquire new fates. To switch from differentiated to toti- or pluripotentiality, plant cells need to undergo reprogramming (Cao and Jacobsen 2002b; Neelakandan and Wang 2012) the process that assumes the conversion of a differentiated somatic cell to the dedifferentiated without passing through the cell cycle (Hirochika et al. 1996b) followed by redifferentiation (Grafi 2004). Thus, the dedifferentiation means the withdrawal from a given differentiated state into a state where cell's developmental potency increases (Fehér 2019) and may loss of epigenetic markers-specify (Tanurdzic et al. 2008). Epigenetic variation has been reported during and after being exposed to in vitro culture conditions (De-la-Peña et al. 2012) during cell differentiation and dedifferentiation in plant regeneration systems (Yang et al. 2013).

A change in chromatin organization accompanies the dedifferentiation stage. The portion of heterochromatin in somatic cells becomes euchromatin, and a new balance between the two is established altering gene expression. The process is conveyed by the reduction and/or lack of coordination of DNA methyltransferases and 5-methylcytosine glycosylases expression. Under downregulation of the genes usually, genome-wide (epi)genetic instability was observed. However, when the genes are upregulated genetic stability is maintained (Zhang et al. 2009). Moreover, expression of genes for histones and histone variants, as well as genes involved in post-translational modifications and chromatin regulation (histone methyltransferases and histone deacetylases), increases in suspension cells (Chiu et al. 2010). These changes were linked to the expression patterns of genes for non-coding RNA epigenetic systems (heterochromatic RNA silencing and RNA-dependent DNA methylation). Additionally, the decrease in the RNA endonuclease DCL1 (processor of microRNA precursors), ARGONAUTE family (e.g. AGO1 catalyzing microRNA target transcript cleavage and transcriptional repression) and AGO2 (binds to 21-nt small RNAs), is post-transcriptionally regulated by miR403 (Mallory and Vaucheret 2010) that suppresses its level if AGO1 is present (Harvey et al. 2011).

Firstly, it was thought that miRNAs contributed to cleavage of the homologous transcript (via ARGONAUTE 1 activity). However, miRNAs also act as transcriptional repressors (mediated via AGO1 and AGO10) (Brodersen et al. 2008) and guide DNA methylation in plants (Chellappan et al. 2010). It is evident that trans-acting siRNAs (tasiRNAs) and miRNAs are essential regulators of plant development (Poethig 2009). They participate in physiological regulation and stress tolerance (Sunkar 2010). Moreover, microRNA genes, as well as their biogenesis, are susceptible to aberrant regulation in vitro (Rodriguez-Enriquez et al. 2011). An example of such regulation was described for micropropagated strawberry, where during in vitro culture, the miR156 is upregulated whereas other miRNAs (miR164, miR172, and miR390) are down-regulated (Li et al. 2012). miR156 is one of the eminently conserved plant microRNAs (Axtell and Bowman 2008) and is involved in many fundamental biological processes that include for example plant phase changes (Massoumi et al. 2017; Wu et al. 2009), stress response (Matthews et al. 2019) or regulating somatic embryogenesis induction (Long et al. 2018; Szyrajew et al. 2017). Thus, under in vitro conditions, various miRNAs even from the same family, may differ in their expression manner. Also, the regulation of miRNAs is controlled by different factors in the culture media, such as auxins, allowing differentiated tissue to reach the growth potential (Us-Camas et al. 2014). Epigenetic regulation may contribute to the tissue culture-induced variation and may lead towards fixed changes at the DNA methylation level.

DNA methylation pattern alterations

Alterations of DNA methylation and/or the DNA methylation status maintenance is the balance between DNA demethylation and de novo methylation. Different sets of enzymes direct each of the processes. It was long thought that DNA demethylation in plants was not an active process. It was assumed that disrupted maintenance of DNA methyltransferases might result in a decreased level of DNA methylation. However, there is evidence that DNA glycosylase-lyases may participate in an active mechanism (Piccolo and Fisher 2014). In plants, such enzymes were first identified in Arabidopsis and are called HhD-GPD (helix–hairpin–helix—Gly/Pro/Asp) DNA glycosylases. The enzymes are responsible for the recognition and excision of bases modified or damaged by oxidation, alkylation, and deamination (Fromme and Verdine 2004). They seem to be involved in transcriptional silencing (Choi et al. 2002; Gong et al. 2002).

In plants, there are separate sequence contexts subjected to demethylation (Gehring and Henikoff 2008) including the symmetric (CG, CHG), and asymmetric (CHH; where H is A, C, or T) ones (Gehring 2013). The demethylation controlled by the DNA glycosylase-lyases is performed via the excision of 5mC of fully or hemimethylated substrates with specificity towards CG, CHG or CHH sites. While HhH-GPD DNA glycosylases are the largest class of glycosylases among all organisms, the DME family appears to be unique to plants. However, how 5-methylcytosine DNA glycosylases recognize their substrate is not apparent. One possibility is that they recognize the ends of genes (Gehring and Henikoff 2008).

The process opposite to demethylation is called de novo methylation. It may take place after DNA replication using a maintenance class of DNA methyltransferases (DRM2, MET1, and CMT3) recognizing the methylation marks on the parental strand of DNA and transferring methylation to the daughters' strands (Cao and Jacobsen 2002a). Alternatively, de novo methylation may involve RNA-directed DNA methylation (RdDM) accompanied by the action of the DRM2 de novo DNA methyltransferase (Miki and Shimamoto 2008). The post-replication mechanism of DNA methylation is common for the symmetric CG, CHG sequences (by MET1, CMT3 methyltransferases, respectively (Gehring 2013), whereas the DRM2 maintains asymmetric sites that require siRNA guide and reestablishment after each cycle of DNA replication or CMT2 (Du et al. 2012; Law and Jacobsen 2010; Matzke and Mosher 2014). The CMT3 and DRM2 are capable of methylating non-CG sites. The methyltransferases (MET1, CMT3, and DRM2) maintain existing DNA methylation patterns. However, only the RdDM pathway, involving numerous RNAs (Wendte and Pikaard 2017) establishes the mark in all sequence contexts (Greenberg 2012).

At the DNA level, the DNA methylation alterations are usually common in the case of the in vitro tissue culture-induced variation (Machczyńska et al. 2015). In some species, they may reach up to several percentages of detected changes (Bednarek et al. 2007; Fiuk et al. 2010; Machczyńska et al. 2014a). The in vitro tissue culture-induced DNA methylation pattern alterations were described, for example, in maize (Brown 1989) and rice (Müller et al. 1990; Zheng et al. 1987). They were also detected in the rye (Aydin et al. 2016), triticale (Bednarek et al. 2017; Brown 1989; Machczyńska et al. 2014a, b, 2015) or barley (Bednarek et al. 2007; Orłowska et al. 2016). Depending on the species the increase (Bednarek et al. 2007; Fiuk et al. 2010) or decrease (Bednarek et al. 2017; Machczyńska et al. 2014a, b, 2015) in DNA methylation level was documented. It was also noted that, at least in garlic (*Allium sativum*), the genetic changes accumulated along the time of in vitro culture, whereas epigenetic (CG demethylation and methylation) once stabilized within initial 6 months of the in vitro tissue cultures (Gimenez et al. 2016).

It is being assumed that in vitro propagation passing through callus phase (e.g., somatic or androgenesis) is prone to (epi)genetic changes among the regenerants (Miguel and Marum 2011; San et al. 2018; Vining et al. 2013) possibly due to the fact that the dedifferentiation process may not be complete (Rodriguez Lopez et al. 2010). It was demonstrated that regenerants derived via somatic embryogenesis from leaves of cacao (*Theobraroma cacao*) retained the C-methylation pattern of the explant tissue. Thus, the DNA methylation pattern was not entirely wiped during callus phase and was partially preserved in regenerants (Kitimu et al. 2015) leading to somaclonal variants. Moreover, variation in DNA methylation between lines established from different nodes on the same parent plant was reported (Baranek et al. 2010). Furthermore, DNA methylation changes were evaluated under in vitro conditions in the early embryo stages leading to defects in gene expression and development (Deshmukh et al. 2011; Fernández-Gonzalez et al. 2007; Reis e Silva et al. 2012). Dedifferentiation of specialized mesophyll cells of *Arabidopsis thaliana* into protoplasts resulted in a dramatic reduction of heterochromatin decondensation of major repeats except for the 45s rDNA one (Tessadori et al. 2007). The process could be reversed upon prolonged culturing. The hypermethylation of euchromatic DNA was described in a long-term cell suspension of *Arabidopsis thaliana* (Tanurdzic et al. 2008). Rapid and reversible changes in DNA methylation were also shown in potato cell suspension (Law and Suttle 2005). Lowered genomic DNA methylation of regenerants derived from shoots compared to young leaves or petals was described in case of bush lily (*Clivia miniata*), suggesting that the variation in methylation of regenerated plantlets was related to the nature of the explants (Wang et al. 2012).

While some (epi)mutations arise spontaneously (Rapp and Wendel 2005; Sano 2002) the others seem to be not random. The so-called hotspots of DNA methylation pattern shared among regenerants and arising during in vitro tissue culture were described (Bednarek et al. 2007; Han et al. 2018; San et al. 2018). The notion of the presence of preferred sites for epimutations is supported by Tanurdzic et al. (2008). Such sites could arise in response to environmental signaling under in vitro culture conditions at specific genic regions (Us-Camas et al. 2014). It could be speculated that such regions should not be covered with proteins, or they may reflect some genomic regions that surmount stresses. The data is consistent with the hypothesis of the presence of a particularly labile portion of the genome susceptible to the stress imposed during tissue culture (Oh et al. 2007).

Extensive and transgenerational epigenetic remodeling associated with plant tissue culture was described in the literature (Hirochika et al. 1996b; Liu et al. 2004; Stroud et al. 2013). In some cases, the DNA methylation changes were inherited by the regenerants' progeny (Han et al. 2018; Koukalova et al. 2005; Zhang et al. 2014). Moreover, the inheritance of alterations among successive progeny depended on species. In triticale, the methylation pattern decreased during several generative cycles following its partial reestablishment (Machczyńska et al. 2014a), in barley, the level of DNA methylation remained unchanged after initial increase among regenerants compared to the explant donors. Interestingly, no morphological variants both among regenerants and the progeny were observed (Bednarek et al. 2007; Machczyńska et al. 2015; Orłowska et al. 2016).

However, others showed that such variants linked to DNA methylation change could arise and were related to morphological differences between oil-palm somatic embryos (Sianipar et al. 2008), physiological change in rice (Akimoto et al. 2007) and cell wall differentiation state in sugar beet cell lines (Causevic et al. 2005).

Transposons

It is becoming evident that expression and movement of transposable elements (TEs) are under epigenetic control necessary for proper genome functioning (Le et al. 2015). Multiple epigenetic pathways silence TEs in plants (Law and Jacobsen 2010) depending on the chromosome region (coding, non-coding) they occupy. Methylated and silenced TEs originate mostly from genic regions, possibly reflecting a compromise between TE silencing and gene expression (Hollister and Gaut 2009). Active genes are mostly methylated at CG sites, whereas silenced TEs in all contexts, including non-CG methylation reflecting inactive heterochromatin (Cokus et al. 2008; Lister et al. 2008). Genes within the vicinity of silenced TEs usually have a low expression (Hollister and Gaut 2009). Still, there are considerable numbers of intragenic TEs in plants (West et al. 2014).

Furthermore, numerous factors required for transcription of genes containing heterochromatic domain have been identified in plants (Coustham et al. 2014; Lei et al. 2014). Moreover, the intragenic TEs are less methylated than intergenic TEs in CG and CHG contexts, while this difference between intronic and exonic TEs was not observed (Le et al. 2015). Also, even longer TEs than those identified within intergenic and intragenic genome regions, were less methylated, in almost all sequence contexts. Possibly though there is selection against methylated TEs in intragenic and proximal regions, due to a downregulated expression of methylated genes (Le et al. 2015), alternatively, pseudogenization may explain the lower expression level of genes with TE insertions (Yang et al. 2010). However, the hypothesis was not confirmed in the case of intronic TEs (Le et al. 2015).

Moreover, some epigenetic mechanisms may neutralize such TEs. Thus, the RdDM pathway may selectively remove TEs from genic regions. Additionally, the intronic TEs are not strongly activated in epigenetic mutants, including *met1* and *ddm1* (Le et al. 2015), suggesting that heterochromatic epigenetic marks carried by intronic TEs might be necessary for correct transcription of associated genes as shown in the case of transcription of exons downstream of heterochromatic domains (Lei et al. 2014). Likewise intergenic TEs, intragenic TEs are recognized by the epigenetic factors maintaining CG and non-CG methylation, even within the actively transcribed regions. Thus, both RdDM-dependent and -independent pathways may participate in DNA methylation of intragenic TEs in case of small euchromatic and long heterochromatic elements (Zemach et al. 2013).

TEs mobility is under epigenetic control of the host genome. Nevertheless, some elements may escape epigenetic silencing, if they are AT-rich and thus, target AT-rich genomic regions (Naito et al. 2009). Another option is targeting to transcriptionally silent heterochromatic regions as described for *Ty3-gypsy* retrotransposons (Gao et al. 2008). Remarkably, some TEs may self-regulate their activity in response to stress by gaining stress-responsive motifs recognized by host regulatory proteins. It was shown that TEs are activated due to, e.g., elevated temperatures (Cavrak et al. 2014), cold, drought, salinity, wounding, UV light, pathogen attack (Grandbastien 2015), due to interspecific hybridization and polyploidization (Vicient and Casacuberta 2017) and tissue cultures (Azman et al. 2014; Cheng et al. 2006). However, in the latter case, the contrasting data are available (Planckaert and Walbot 1989).

It has been evidenced that epigenetic changes that occur through the culture process are responsible for the activation of transposable elements (Azman et al. 2014; Grzebelus 2018; Ishizaki and Kato 2005; Miyao et al. 2011; Neelakandan and Wang 2012; Sabot et al. 2011). However, this is not always the case (Ishizaki and Kato 2005; Orłowska et al. 2016). In studies on Arabidopsis, no transposition of TEs was detected (Jiang et al. 2011). The same was also demonstrated for some TEs in barley (Orłowska et al. 2016). However, in the regenerants of rice (Miyao et al. 2011; Sabot et al. 2011), and barley (Orłowska et al. 2016), several TE families were active. In other studies, also on rice, remodeling of cytosine methylation of *Tos17* (5′LTR region), possibly due to the RNA-directed DNA methylation pathway responsible for repressive control of *Tos17*, was detected as the result of tissue culture (Zhang et al. 2014). Moreover, tissue culture-induced TE activity has been widely reported in various plant species (Hirochika et al. 1996a), rye (Alves et al. 2005), maize (Barret et al. 2006; Geiger 2009) and rice (Huang et al. 2009; Picault et al. 2009). Conceivably, specific stresses activate some transposons (Cavrak et al. 2014), whereas others are activated in other different cases (Ikeda et al. 2001).

At least under some conditions, the host control over TEs is reduced and to some extent could be reestablished in the progeny as demonstrated for barley regenerants derived via anther cultures and their generative progeny (Orłowska et al. 2016). The burst of TEs activity is different from single nucleotide mutations as they are generated at a relatively constant rate per generation. In the case of active MITE family up to 40 new changes per plant per generation were observed (Naito et al. 2009) exceeding the rate of point mutations. Thus, although retrotransposon activity is considered to be one of the causes of variability induced in tissue cultures, it should be emphasized that they can also be

responsible for pre-existing variation (Peschke et al. 1987) and with higher rearrangement and mutation rates within specific genome regions (Oh et al. 2007).

Among TEs that can be studied in tissue cultures in cereals, the group of long terminal repeats (LTR) and the non-LTR retrotransposons seems suitable (Flavell et al. 1992; Suoniemi et al. 1998). For example, BARE-1 has homologs in different species e.g., barley, oat, wheat, or rye (Gribbon et al. 1999; Pearce et al. 1997). Moreover, its activity, linked to the in vitro tissue cultures and DNA methylation (Chandler and Walbot 1986; Chomet et al. 1987) is also documented in barley (Orłowska et al. 2016). Moreover, TEs movement may be a source of mutations, duplication, and rearrangements transmitted to the progeny or their movement may influence gene expression. They may also contribute to genome instability (Walbot and Cullis 1985) observed, e.g., among triticale regenerants derived via anther tissue cultures (Oleszczuk et al. 2011).

In vitro phenomena regulated by epigenetic processes

The habituation, rejuvenation, and morphological changes (Smulders and de Klerk 2011) are the in vitro phenomena regulated by epigenetic changes in plants. Subculturing and the habituation are among the negative factors that spur epigenetic and phenotype changes, which can be heritable (Meins 1989; Peredo et al. 2006) but reversible (Meins and Foster 1985; Smulders 2005; Smulders and de Klerk 2011). Meins and Thomas (2003) demonstrated that cultured tobacco cells exhibited a constitutive cytokinin-habituated phenotype that was avoided in some regenerated plants. Thus, changes in DNA methylation during in vitro plant regeneration might be responsible for the phenomenon. The role of DNA methylation seems to be confirmed in studies on the transcriptome-based characterization of habituated and non-habituated cell culture of *Arabidopsis thaliana* (Pischke et al. 2006). The Authors analyzing differences in regulation of methyltransferase MET1, chromomethylases CMT1, and CMT3 suggested that there is a precise regulation in methylation patterns between habituated and non-habituated cultures.

In many cases, the method of regeneration in PTC leads to the formation of callus, a mass of proliferating cells, that may appear e.g. after injury, in de novo organogenesis and in somatic embryogenesis (Sugimoto et al. 2011). The tissue culture environment rich in various plant hormones triggers the callus cells to produce organized structures like roots or shots that end up with regenerants. The formation of callus in PTC conditions undergoes epigenetic control involved changes in chromatin structure (DNA methylation, histone modification, and deposition) (Lee and Seo 2018). Firstly during callus formation is observed the burst of hypomethylation in symmetric (CG, CHG) and asymmetric (CHH) contexts (Zakrzewski et al. 2017). Such phenomena favored the movement of mobile elements while the callus is formed (Lanciano et al. 2017) what may lead to genomic instability as in case of rice plants regenerated from tissue culture (Stroud et al. 2013). The acquisition by callus of the pluripotent properties may proceed via histone modification. In studies devoted to Arabidopsis shoot regeneration competency Authors described the mechanism how during callus formation LYSINE-SPECIFIC DEMETHYLASE 1-LIKE 3 (LDL3) specifically demethylated dimethylated lysine 4 of histone H3 (H3K4me2) (Ishihara et al. 2019). That epigenetic mechanism let callus to acquire shoot regenerative competency. Also, global changes in the deposition of histone variants (H1A, H1B, H2A.Z, H3.3) are involved in cellular reprogramming (Jullien et al. 2012). The histone variant H2A.Z, which is conserved among eukaryotes, is also involved in callus formation in rice (Zhang et al. 2017). Zhang et al. (2017) underline that the occupancy of H2A.Z is associated with H3 lysine 4 trimethylation (H3K4me3) and H3 lysine 27 trimethylation (H3K27me3) histone marks in callus and seedling tissues. Also, the deposition of H2A.Z is negatively correlated with genes participates in rice tissue development. Summing up the in vitro callogenesis is tightly associated with DNA methylation as well as with histone modification. The epigenetic marks are essential for cell fate reprograming from mature not differentiated tissue to pluripotent root stem cells that may have the ability to regeneration (Berger et al. 2018).

Genetic changes in tissue cultures

For many years, there was a belief that the genetic variation occurring in regenerants could be induced de novo as a result of tissue culture environment or its source may originate from explant as a "pre-existing" variation (Larkin and Scowcroft 1981). Studies conducted on *Saintpaulia* stressed that the variability observed in regenerants might both come from the explant as "pre-existing" variation as well as de novo, and moreover, it turns out that among the mentioned variation types, predominant changes occur during the tissue culture (Sato et al. 2011).

Obtaining plants through tissue cultures is burdened with the appearance of changes of various nature. One of many types of these changes is genetic variation, manifested in the increased frequency of point mutations (Jiang et al. 2011), in chromosomal breakages (Dogramaci-Altuntepe et al. 2001), and in the activation of mobile elements (Ong-Abdullah et al. 2015). What's more, the coexistence of genetic and epigenetic changes promoted by in vitro culture in regenerated crop plants (rye, barley, triticale, wheat, rice, corn) was documented (Baranek et al. 2016; Bednarek et al. 2007; Linacero et al. 2011;

Machczyńska et al. 2015; Wang et al. 2013; Yu et al. 2011). Through the use of methylation-sensitive restriction enzymes, it was determined that genetic changes occurred in 73% (Aile's cultivar) and 30% (Merced cultivar) of the rye plants, while epigenetic changes happened in 50 and 73% of the Aile's and Merced cultivars, respectively (Linacero et al. 2011). It was also found that the genetic variation was related to the presence of the CCGG targets, suggesting that there is a common mechanism connecting genetic and epigenetic phenomena. Some authors postulate that discrimination between genetic and epigenetic changes that appeared in tissue cultures is tricky (Smulders and de Klerk 2011; Vázquez 2001). The example of such tangled mechanisms is the activation of mobile elements. DNA methylation is the most important epigenetic mark that preserves the genome against TE disruption (Zakrzewski et al. 2017).

Among genetic changes affecting the regenerants, the DNA sequence changes, as well as gene amplification, transposition, and chromosomal alterations, are the most common. Chromosomal changes include several different phenomena such as disturbed ploidy and chromosome number as well as changes in chromosome architecture (duplications, translocation, deletion and inversions of chromosome segments). Moreover, Kaeppler and Phillips (1993) underlined that changes in chromosome architecture are more common than in chromosome number in plants derived via tissue culture. In studies devoted to potatoes (*Solanum tuberosum*) regenerated from either protoplasts or stem explants, all regenerants revealed aneuploidy or structural chromosomal changes. Between structural changes, there were segmental deletions and duplications (Fossi et al. 2019). In the case of potato, the tissue culture environment caused genomic instability that may end up with altered plant phenotype.

The genetic variation related to DNA sequence changes is frequent in plants obtained via tissue culture although it does not have to manifest in phenotypic level (Machczyńska et al. 2014b; Orłowska et al. 2016). Single base pair changes may appear as a result of deamination of methylated cytosine to thiamine that leads to transition (Brettell et al. 1986). DNA point mutations may have many sources, among them, are polymerase errors during DNA replication, incorrect mismatch repair mechanism, DNA damage made by ROS, light, UV or deamination of methylated cytosine (Maki 2002). Comparison of frequency between genetic changes and alteration at the chromosomal level showed that the first one is more ubiquitous in regenerants (Kaeppler et al. 1998). In many cases, the precise nature of the DNA point mutation is unidentified as such kind of changes are frequently detected indirectly via PCR and electrophoresis mode (Jin et al. 2008).

Moreover, the frequency of tissue culture-induced base substitution is much higher than the expected spontaneous mutation rate (Rodríguez López et al. 2010). Otherwise, some bases are more mutable than others, and transitions are more frequent than transversions (Wang et al. 1998). Moreover, point mutations in plant tissue cultures are generally of the same kind as those occurring in vivo (Rodríguez López et al. 2010).

Conclusions

In the given review, we have focused on some aspects of cell functioning under stress conditions that may participate in the induction of the so-called TCIV or SV. We have tried to give a comprehensive overlook of how the stressing factors may influence the cell wall and membrane inducing signal that is transmitted to cellular organelles and then discussed (epi)genetic mechanisms working in the nucleus. Moreover, the current state of knowledge summarizing the role of a wide range of chromosomal changes was presented.

Author contributions PTB and RO compiled the literature sources and wrote the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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