REVIEW ARTICLE

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Genetic Relationship of Transcriptional Factor Genes in the Regulation of Cells Death in Arabidopsis: A Review

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ABSTRACT

The leaf yellowing is the first visible sign of senescence, which starts at the margins of the leaf and progresses to the blade. Although, transcriptional factor family genes generally encode meticulous regulators which perform a range of functions in turns regulating the physiological and developmental mechanism of plant stature. However, the genetic relationship of *TFs* genes in regulating the cell death of *Arabidopsis* is well not understood to date. *TFs* family in a plant regulates various developmental and stress responses in underline pathways. In our review we observed the genetic relationship of *TFs* genes in regulations of cell death in *Arabidopsis*. Given that, programmed cell death (PCD) being an active process that includes the expression of hundreds of genes. It is speculated that many *TFs* are involved in the core elements of the regulatory network. There are only a few factors that are being demonstrated in involving the regulation of cell death, by evaluating the leaf senescence appearances of knocking of mutants and by identifying downstream target genes. In this review, we have focused on the manifold roles of *TFs* during genetic relationships and the regulation of cell death in *Arabidopsis*. We also deliberated how the transcription factors family gene regulates the cells' death by different hormonal stress, environmental strain and their role in retrograde signaling. For deep understanding of regulatory molecular mechanisms of cell death in the plant, future research may be hypothesized to collect appropriate evidence and a detailed study may be implemented on the upstream pathway with a specific targeted gene that recognizes the stress signals involved in cell death in plants. Also, crosstalk between mitochondria and chloroplast is mainly being focused to better understand the regulations of cell death in plants. Present review concludes that regulating the cell death of *Arabidopsis* is very important for meeting future global food needs, crop yields. Overexpression of *ERF* transcription factors genes relating cell death of *Arabidopsis* confers broad-spectrum resistance to pathogens and other abiotic stresses and can also make transgenic plants resistant to drought, salinity and freezing.

Key words: *Arabidopsis*, AP2/ERF, Cells death, Stress, Transcriptional regulation.

Aging is a highly complex process involving the cessation of chloroplasts, the decay mechanism of photosynthesis and the degradation of macromolecules like lipids, protein and nucleic acids (Buchanan-Wollaston *et al*., 2005). The first visible event during aging so far is that the leaves turn yellow, which usually begins at the leaf edge advances to the blade (Quirino *et al*., 2000). Integrated response of leaf cells namely leaf senescence provides information about age and many other external and internal signals (Yoshida, 2003). This comprehensive aging retort offers an optimum adaptation to plants by fine-tuning the onset time, rate of progression and the nature of leaf senescence by incorporating the plant's endogenous status into a given ecological environment (Lim *et al*., 2007). There are various abiotic as well as biotic factors that are influencing leaf senescence (Chen *et al*., 2002). To reproduce and survive under adversative situations, plants develop a variety of adaptive traits that are controlled by complex systems. Interconnected diverse networks operating in the downstream signaling cascade are regulated by transcriptional factors combined with cis elements present in their promoters. The knocking out genes relation also has a significant role in the senescence of any plant's organs, such as fruits, flowers as well as leaves (Lin and Wu, 2014).

ERF is one of the chief transcriptional factors in plants that regulates many stresses and progressive response pathways (Li *et al*., 2015; Licausi *et al*., 2013). Thus, in our present hypothesized review, we pointed-out to observe the genetic relationship of *AtERFs* genes in regulations of cell death in *Arabidopsis*. Given that, Programmed Cell Death (PCD) including the expression of hundreds of genes, whereby several transcription factors act as core elements for the regulatory network (Guo *et al*., 2004). Using genome-

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wide analysis, several *Arabidopsis* genes can be identified through encoding the transcription factors like up-regulation in leaves' aging (Balazadeh *et al*., 2008; Buchanan-Wollaston *et al*., 2005). There are only a few factors that are being demonstrated in involving the regulation of cell death, by evaluating the leaf senescence appearances of knocking of mutants and by identifying downstream target genes. In this review, we will focus on the manifold roles of *TFs* during genetic relationships. We will also deliberate how the Transcription factors family gene (*ERF*) regulates the cell's death by different hormonal stress, environmental strain and their role in retrograde signaling. These emergent complexity needs to be discussed first to explore the commercialized plants and understand the controlled molecular mechanism involved in it. The present hypothesized object is to emphasize the latest advances in this field based on our knowledge to provide a comprehensive overview of the role of these family genes in the *Arabidopsis* plant.

Transcriptional regulations of cells death

Age-related phenomenon namely the aging of plants is meticulously associated with the death of cells. Leaf aging ensures the recycling from aging leaves to young leaves. The primarily plant-specific TFs like ERFs possess around 139 and 122 ERF family genes in *Arabidopsis* (Yoshida, 2003; Nakano *et al*., 2006). The number of ERFs in different plants species may be variable: barley-121 (Guo *et al*., 2016), brassica- 291 (Song *et al*., 2013), cassava-147 (Fan *et al*., 2016), cotton Genus-271 species (Lei *et al*., 2016), Solanum-155 (Charfeddine *et al*., 2015) and Triticum-117 (Zhuang *et al*., 2008). The process of aging is heritably linked to the death of cells and involves the regulated expression of genes relating to the cells' death (Lim *et al*., 2007). Microarray studies have revealed that *Arabidopsis thaliana* has shown dramatic alterations in the gene expression patterns during age-reliant senescence (Wagstaff *et al*., 2009). During aging forward, regulation of age-related cell death has been confirmed in the *Arabidopsis*. The transcription factor-like ORESARA1 initiates aging-linked cell death in the leaves of *Arabidopsis* having 28 days of age. However, during senescence, the downregulation of miR164 causes the negative regulation of ORE1 expression by miR164 (Kim *et al*., 2009). Besides ORE1, leaf necrosis also occurs due to higher expression of the WRKY6 transcription factor gene (Robatzek and Somssich, 2002). WRKY6 activates the promoter of the senescence-induced receptor KINASE1, which is specifically induced during the cell death of the leaves (Fig 1 and 2). Likewise, overexpression of the AP3/PI (AtNAP)/ANAC029 gene encoding NAC family transcription factors results from premature aging. The NAC transcription factor ORE1 SISTER1/ANAC059 is a progressive director of aging (Guo and Gan, 2006; Balazadeh *et al*., 2011).

Progression of cells death and genes expression

At present today, the various forms of plant programmed cell death are indisputable during the development and environmental interactions (Wu *et al*., 2014), limited information is available about molecular regulatory mechanisms of these processes. Though during the plant life cycle, cell death will be induced in various circumstances, it is not clear to date whether a common mechanism controlling different PCD types. During reports citations, we have found that numerous genes encoding nucleases, including BFN1, CAN1 and RNS3 are involved in transcriptionally regulated genes during differentiation-induced cell death. Though BFN1 is a renowned leaf senescence gene which too plays a significant part in the breakdown of chromatin in the root crown cells (Fendrych *et al*. 2014). CAN1 is a plasma membrane-bound nuclease relating to the Staphylococcus, whose expression was previously accompanied by the cell's death (Ito and Fukuda, 2002), but its actual role is still unclear. A few reports have revealed that the SAUL1 mutant is deficient in the expression of the E3 ubiquitin ligase gene. SAUL1 looks to has miscalculated evolving age and turn on the adjustment switch for age-related cells seedling death (Fig 1). Though, in wild-type *Arabidopsis*; the age-related involves miR164, ORE1 and EIN2 which ensure that the aging initiates the cells death in leaves. Throughout the leaf development, ORE1 accumulation is achieved by the downregulation miR164 that involve in the ethylene signaling leaf senescence (Bisson *et al*., 2009). Moreover, ORE1 accumulates and SAG12 expression is usually prompted and age-related aging and cell-associated death can be noticed hastily Thus SAUL1 prevents cell death (under low light conditions) in the wild-type plants. Nonetheless, through genetic analysis, ORE1/ANAC092 in saul1-1/anac092-1 double mutant did not cause inhibition of the saul1 phenotype (Fig 1 and 2). The higher ORE1 expression itself is not adequate for causing the cells' death and saul1 aging in plants (Lesniewicz *et al*., 2012).

Senescence associated incidences and signaling

Premature senescence reduces the yield of annual crops while delaying senescence has a positive and negative impact on yield and nutritional quality. Genomic studies of leaf senescence-related to *Arabidopsis* have been very efficacious in screening for mutants that have been impaired during senescence. The studies of influenced genes provide perceptions of the molecular basis of leaf senescence (Liu *et al*., 2011). However, no obvious senescence phenotype was observed in most of the senescence-associated mutant genes (SAG) recognized by the reverse genetic approach (Jing *et al*., 2005; Li *et al*., 2012). The expression of many senescence-associated genes (SAGs) is up-regulated during senescence, while the expression of photosynthesis-associated genes (PAGs) is down-regulated (Fig 1). Investigations on the SAGs have indicated a complex regulation of leaf senescence (Nam, 1997; Gan and Amasino, 1997). The age of individual leaf plays a significant role in determining the longevity of leaf in *Arabidopsis* (Lim *et al*., 2007; Jing *et al*., 2002). Floral initiation can affect the longevity and senescence of plants (Levey and Wingler,

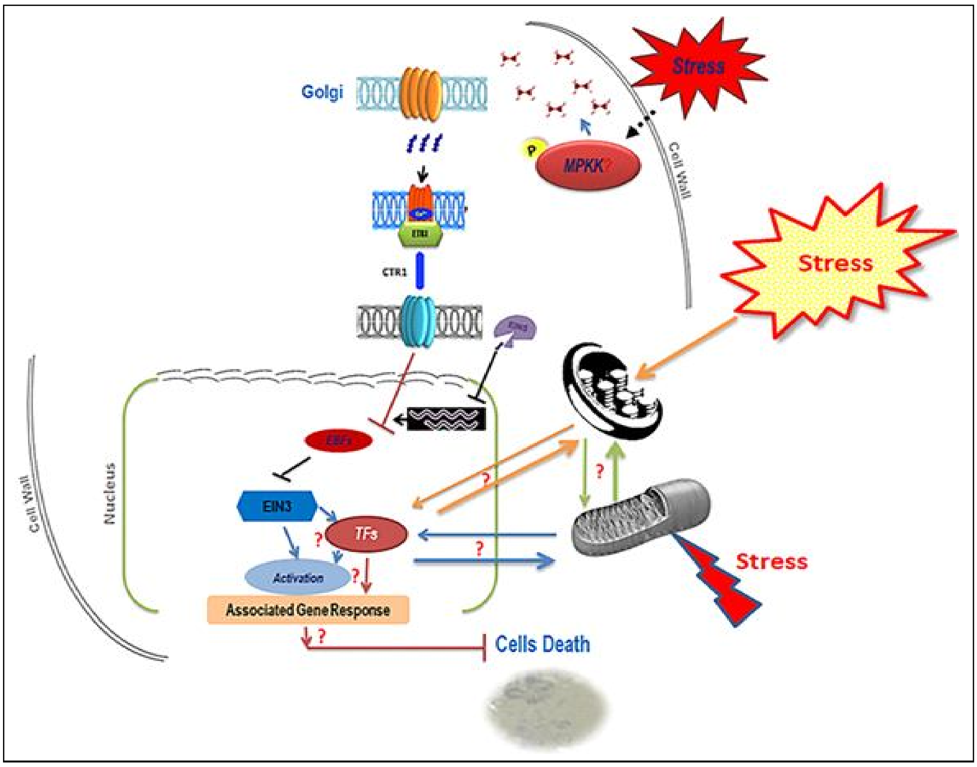

Fig 1: Schematic regulatory network of associated genes response in modulating cell death. Illustrative proposed hypothesized model representing the regulation of cell death encoding genes at *TFs* level during stress responses.

2005; Nooden and Penney, 2001). Certain to that, the findings also support accelerated and initiated leaf senescence, which is used to reduce chlorophyll content in silent plants (Lim *et al*., 2007; Quirino *et al*., 2000; Hee *et al*., 2010). Besides, other family plant transcription factors usually have comparable roles. For example, the WRKY and NAC family genes are aging linked to well-known transcription (Fig 2). During the development of activated senescence in the *Arabidopsis*, more than 20% of the 109 NAC family genes are explicitly tempted. Combining all these observations, the profile of transcription factor findings indicate that the cue agent can play a directing role in the initiation of cells death signs and leaf senescence singling, whereas using the transcriptional activation or inhibition of genes involved in the leaf development it can control the senescence (Buchanan-Wollaston *et al*., 2005).

Functions of age-dependent associated Genes and network in cells death

Leaf senescence advances with age, where the process includes complex regulation of the premature life stages of the leaf as well as many exogenous and endogenous factors (Buchanan-Wollaston *et al*., 2005). There are a lot of SA genes whose coordinated expression regulates the plant senescence. By identification and characterization of several SA genes and many aging concerned mutants, a major molecule breakthrough has been explored through this phenomenal understanding. The transcription genes function as a progressive regulator in the age of reliant leaf

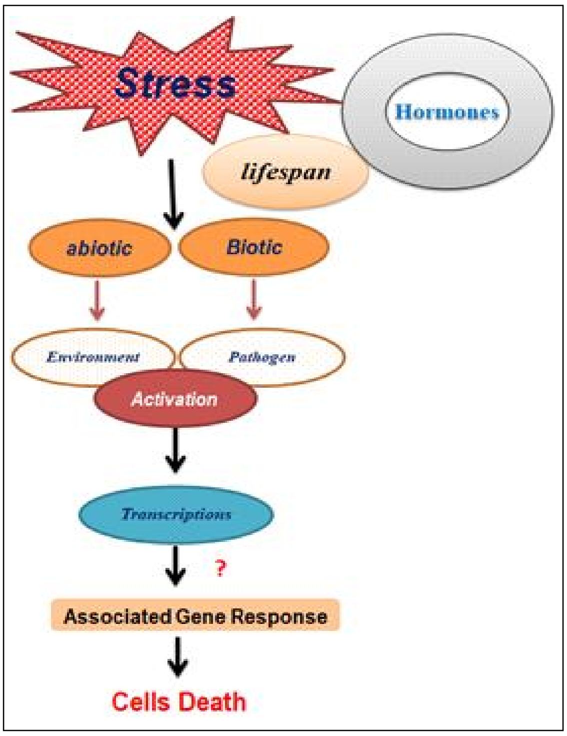

Fig 2: Successive signs of different molecular steps indicate cell death. The proposed model shows that cell death events are part of cell differentiation triggered by hormonal signaling. This results in transcriptional activation of cell death-associated genes such as *TFs*. Besides, cells death is only initiated after a cell death trigger.

senescence. They interact with the *RGL1*, however, *RGL1* impedes the transcriptional function of WRKY45 (Table 1). Moreover, several transcription factors are also prompted during the transcription stage, though combinable suggest the directing role of complex transcriptional regulatory networks in the leaf senescence (Liu *et al*., 2011). It will be very interesting, in the forthcoming future, to identify the possible modifications in aging and aging correlated proteins, which will offer further understanding of leaf senescence and cell death mechanisms. Further, the leaf aging of any plant leads to the identification of thousands of SA genes (He *et al*., 2001), while the utmost SA genes mutations modify the leaf senescence (Fig 1 and 2). It may be due to the functional termination aging process (Li *et al*., 2012). At the same time, the forward genetics approach in *Arabidopsis* has been determined in a group of leaf senescence concerned genes like ORE genes (Lim *et al*., 2007; Jing *et al*., 2005; Woo *et al*., 2001) and death regulating genes of plant leaves (Guo and Gan, 2006; Kim *et al*., 2009). Presumed those molecular mechanisms of controlling plant senescence and cell death have wide-ranging prospects for improving crop yield potential and nutritional quality under optimal and stressful conditions. While, many *TFs* families, particularly those from the NAC, WRKY and ERF families (Guo *et al*, 2004; Breeze *et al*., 2011) exhibited an effect of modulating senescence. Reports suggested that different genes identified in the NAC transcription family *viz.* ORE1, AtNAP, ORS1, ATAF1, NTL4, WRKY53 and WRKY22 to regulate the senescence and cell death in *Arabidopsis* leaves (Gregersen and Holm, 2007; Miao *et al*, 2004) (Table 1).

Role of different hormones in regulation of cells death

It is reported that the regulation of phytohormones serves as an endogenous signal, including senescence and cell death almost in all prospectuses of plant growth and development. Abscisic acid (ABA), Auxin, Jasmonic Acid (JA), Ethylene, Cytokinin and Gibberellin (GA) play important roles in promoting or inhibiting aging dependent activities (Cai *et al*., 2002; VanDoorn, 2008). Further, the significant effects of hormones on the regulation of cell death of plants are briefly described below:

Ethylene regulates the cell death

It has been reported that the regulation of ethylene serves as an endogenous signal including senescence in almost instructions for plant growth and development (Chen, 2011; Van Doorn, 2008). The aging is accompanied by a sudden and transient increase in respiration associated with increased ethylene production (Xu and Hanson, 2000). In Dianthus, exposure to ethylene causes premature senescence of petals and increases or decreases the abundance of mRNA populations, suggesting that physiological changes in petals may be the result of rapid changes in gene expression (Ahlfors *et al*., 2004; Huang *et al*., 2007). As earlier revealed that the ethylene is a necessary regulator of the cell death pathway triggered in the vad1-1. In contrast, in the mutant vad1-1 the degree of cell death was increased and in cells that overexpressed ERF1; a positive regulator of ethylene response and CTR1; a negative regulator of ethylene signaling; in the CTR1 mutant the death time consistently increased. In this regard, the

Table 1: Associated genes of cells death in different species of plants.

Gene	Plant species	Regulation	References
SAUL1 Mutants	*Arabidopsis*	Regulates early senescence and cells death	Katja *et al.* 2012
ANAC092	*Arabidopsis*	Aging-associated cells death	Kim *et al*., 2009
WRKY6	*Arabidopsis*	Leads to leaf cells death	Robatzek and Somssich, 2002
WRKY22	*Arabidopsis*	Regulation of cells death	Zhou *et al*., 2011
WRKY70	*Arabidopsis*	Regulation of cells death	Ulker *et al*., 2007
ANAC029	*Arabidopsis*	Regulates early senescence and cells death	Guo and Gan, 2006
ATNAP mutant	*Arabidopsis*	Positive regulator of senescence	Balazadeh *et al*., 2011
ORE9	*Arabidopsis*	Positive regulator of leaf senescence	Woo *et al*., 2001
GRI	*Arabidopsis*	Regulation of cells death	Zhonghai *et al*., 2013
WRKY33	*Arabidopsis*	Defense response	Ulker *et al*., 2007
RAV1	*Arabidopsis*	Positively regulates leaf senescence	Hye *et al*., 2010
CYCLASE1	*Arabidopsis*	Regulations of cells death	Sarah *et al*., 2015
MSL10	*Arabidopsis*	Regulation of Cells death	Kira *et al*., 2014
RGL1	*Arabidopsis*	Regulate age-triggered leaf senescence	Ligang *et al*., 2017
WRKY45	*Arabidopsis*	Regulate age-triggered leaf senescence	Ligang *et al*., 2017
HvS40 family	Barley	Senescence associated marker genes	Muhammad *et al*., 2017
OsS40	Rice	Senescence associated marker genes	Muhammad *et al*., 2017
Ein3	Rose	Senescence-associated gene	Zhonghai *et al*., 2013
NAC	Rose	Induced plant senescence and cells death	Ma *et al*., 2012
PR10	Rose	Induced plant senescence	Wu *et al*., 2018
ANACO32	*Arabidopsis*	Regulations of cells death	Guo and Gan, 2006

use of ethylene accounts for the amplification of superoxide accumulation, thereby promoting the execution of diffusion cell death (Overmyer *et al*., 2000).

Cytokinin induced cell death

Cytokinin (CKs) plays a significant role in cell division, proliferation and differentiation. It participates in several aspects of plant growth including seed sprouting, inhibit the yellowing, differentiation of chloroplast, apical supremacy, as well as aging of cells (Argueso *et al*., 2009; Werner and Schmulling, 2009). It has been recently proved that a high level of CK induces programmed cell death (PCD) in the plant cells (Carimi *et al*., 2003). 6-benzyl amino purine (BA) showed a high frequency of suspension cell culture of several plants including *Arabidopsis*, carrot and alfalfa cells decreased growth and induced cell death (Zottini *et al*., 2006).

Gibberellin (GA) signaling in leaf senescence

The gibberellin (GA) plays an elusive role in the signaling in leaf senescence. Various studies have shown that the influence of GA on leaf senescence depends on the GA dose and the condition of the treated leaf (Chen *et al*., 2011). While this further requires clarification. Investigations have confirmed that the Gibberellin Insensitive Dwarf1 (GID1) GA receptor / Della repressor pathway receives and transduces the GA signal (Sakakibara, 2006). Moreover, Della proteins such as Repressor OF ga1-3 (RGA), GA Insensitive (GAI), RGL2, RGA-LIKE 1 (RGL1) and RGL3, have unique overlapping functions and act as the main repressors of about all GA responses, in the Arabidopsis (Mlejnek and Prochazka, 2002).

CONCLUSION AND FUTURE PROSPECTIVE

To meet future global food needs, crop yields must be increased in challenging environments. With conventional breeding, it is difficult to produce complete and timely resistance to biotic and abiotic stresses. Also, analysis of overexpression of *ERF* genes indicates that these transcription factors can confer broad-spectrum resistance to pathogens and other abiotic stresses and can also make transgenic plants resistant to drought, salinity and freezing. Further elucidating the genes related to senescence will expand the understanding of leaf senescence regulation at the molecular level. Transcription factors are known for their critical function of triggering or inhibiting defense gene expression in signal transduction and for the regulation of connectivity between various signaling pathways. It has been observed that the *ERF* gene is not only stimulated by disease-related and pathogen infection stimulation but also because abiotic stress can trigger its expression level. Therefore, associated such as transcriptional can improve the multiple stress resistance of transgenic plants. Therefore, various challenges should be noted in terms of cold pressure. Elucidating the regulatory and signaling mechanisms of the gene in stress is an important goal to gain a complete understanding of the stress signaling mechanism. However, more research is needed to find out the details of the pathways involved in plant cell death, especially the role of interpreting chloroplasts. For understanding of regulatory molecular mechanisms of cell death in the plant, future research may be hypothesized to collect appropriate information and a detailed study may be implemented on the upstream pathway with a specific targeted gene that recognizes the stress signals involved in cell death in plants. A recent study revealed that the cell death regulatory process may involve the synergetic effects of chloroplast and mitochondria. Therefore, crosstalk analyses between mitochondria and chloroplast are mainly be focused to better understand the regulations of cell death in plants. Also, leaf senescence is an evolutionary developmental strategy. Therefore, we hypothesized that plants aging has evolved in different environmental stress have different physiology and regulation patterns. Thus, a comparative study of various *Arabidopsis* ecotypes and different plants with different aging strategies will be conducted. This will enable us to define the metabolic and physiological processes of aging, the principles of regulation and the evolution of aging and death programs based on the temporal and spatial transformation of molecules, cells and organ networks. Despite this, many important questions remain unclear, such as the nature of the age signal and time measurement system yet unknown. What regulatory network is responsible for functional conversion during the aging process of leaves? The relationship between leaf senescence and other developmental processes are also needed to be understood and further deep study may be made on these aspects. However, a complete understanding of this complex process requires new ideas and techniques. These techniques identify new regulatory factors and mechanisms and generate a set of interesting and important hypotheses that will lead to a better understanding of life-history strategies, including senescence, aging and death.

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