Gene Mining for Proline Based Signaling Proteins in Cell Wall of Arabidopsis thaliana

Muhammad Z. Ihsan, Samina J. N. Ahmad, Zahid Hussain Shah, Hafiz M. Rehman, Zubair Aslam, Ishita Ahuja, Atle M. Bones and Jam N. Ahmad

1 Cholistan Institute of Desert Studies, The Islamia University Bahawalpur, Bahawalpur, Pakistan, 2 Plant Stress Physiology and Molecular Biology Lab, Department of Botany, University of Agriculture Faisalabad, Faisalabad, Pakistan, 3 Integrated Genomics Cellular Developmental and Biotechnology Lab, Department of Entomology, University of Agriculture Faisalabad, Faisalabad, Pakistan, 4 Department of Arid Land Agriculture, Faculty of Meteorology, King Abdulaziz University, Jeddah, Saudi Arabia, 5 Department of Electronic and Biomedical Engineering, Chonnam National University, Gwangju, South Korea, 6 Department of Agronomy, University of Agriculture Faisalabad, Faisalabad, Pakistan, 7 Department of Biology, Norwegian University of Science and Technology, Trondheim, Norway

The cell wall (CW) as a first line of defense against biotic and abiotic stresses is of primary importance in plant biology. The proteins associated with cell walls play a significant role in determining a plant's sustainability to adverse environmental conditions. In this work, the genes encoding cell wall proteins (CWPs) in Arabidopsis were identified and functionally classified using geneMANIA and GENEVESTIGATOR with published microarrays data. This yielded 1605 genes, out of which 58 genes encoded proline-rich proteins (PRPs) and glycine-rich proteins (GRPs). Here, we have focused on the cellular compartmentalization, biological processes, and molecular functioning of proline-rich CWPs along with their expression at different plant developmental stages. The mined genes were categorized into five classes on the basis of the type of PRPs encoded in the cell wall of Arabidopsis thaliana. We review the domain structure and function of each class of protein, many with respect to the developmental stages of the plant. We have then used networks, hierarchical clustering and correlations to analyze co-expression, co-localization, genetic, and physical interactions and shared protein domains of these PRPs. This has given us further insight into these functionally important CWPs and identified a number of potentially new cell-wall related proteins in A. thaliana.

Keywords: Arabidopsis, co-expression, geneMANIA, GENEVESTIGATOR, kinase, proline

THE PLANT CELL WALL

The cell wall (CW), considered as first line of defense in plants, is composed of polysaccharides (cellulose, hemicellulose, pectin), and proteins. These proteins can either be structural or non-structural depending upon their functionality. Since the first report of cell wall proteins (CWPs) in Hydrodictyon africanumin (Northcote et al., 1960), hundreds of proteins have been identified which serve as an integral structural part (about 10% of wall dry weight) and perform multiple functions in various signaling pathways.

CWPs have key importance in sensing environmental stresses and controlling CW dynamics in response to the growth and development of the plant. However, currently we have a limited understanding of the structure, function and interaction of CWPs, and also very little knowledge...
of association of cuticle with plants reactive phytochemicals (Ahuja et al., 2016). Proline rich proteins (PRPs), proline rich extensin like proteins (PRExts), hydroxy-proline rich O-glycoproteins (HRGPs), expansins, and formin like proteins are some of the known classes of CW proteins with covalent scaffold and glycosylation as their known interactions (Boron et al., 2014; Suzuki et al., 2015). Arabidopsis thaliana is a model plant comprising of five chromosomes with 33,542 genes, where 1,605 genes are responsible for the CW development. Out of these 1,605 genes, 252 are responsible for cellulose, 10 for hemicellulose, and 317 for pectin regulation (Albenne et al., 2013). In this review, we have mainly described PRPs, which are the pivotal constituent of the CW together with mining of genes behind these proteins. Along with this, we have attempted to build wired networks to see how these genes co-express and interact in regulating PRPs during the biological and physical processes as well as in determining the molecular functions. We have used the gene mining approach to identify 58 genes located on different chromosomes (Figure 1). These genes are either directly or indirectly involved in the regulation of proline related proteins in the CW under various biotic and abiotic stresses. We have classified these genes into five groups based on their expression for the different structural and functional proteins (Figure 2). Moreover, schematic diagrams (using GeneMANIA and GENEVESTIGATOR) have been generated for the networks of gene co-expression, gene co-localization, genetic interaction, physical interaction, shared protein domains, and predicted interaction (Figures 2–8). A heat map, genome array, Pearson’s correlation coefficient (PCC) and hierarchical clustering are also presented for the selected genes for an estimation of the genetic interactions and their level of co-expressions at different plant developmental stages and in the various plant anatomical parts.

**CELL WALL PROTEINS (CWPS)**

The CWPs are divided into nine classes based on their signaling events (Albenne et al., 2013). They are linked to the several important pathways including lipid and carbohydrate metabolism, structural components, proteolytic and oxidoreductive activity, cell signaling, molecular interaction, miscellaneous, and the proteins with an unknown activity. The CWPs involved in cell signaling, in response to abiotic stresses, have been extensively studied. Under such stress conditions, the major classification of CWPs include the salt overly sensitive kinases, phospholipases, transcription factors, dehydration responsive element binding proteins, C-repeat binding factor, mitogen activated proteins, and abscisic acid responsive element binding factors (Vinocur and Altman, 2005). The involvement of CW in different stress reception mechanisms is not surprising. Kinases are perceived as potential candidates for the CW sensor (Steinwand and Kieber, 2010). Activation of various kinases in response to the changing levels of the same stress has already been well-reported (Kacperska, 2004). In A. thaliana, 26 genes related to the CW associated kinases (CWAKs), and similar functions have been reported (Verica and He, 2002). In addition to the abiotic stresses, CWAKs are also involved in the plant defense against pathogens (Bellincampi et al., 2014). Recently, a number of new CWAKs have been reported, which include proline rich extensin like receptor kinases (PERKs), leucine rich repeats receptor like kinases (LRKs), and lectin receptor kinases (LeRKs) (Wolf et al., 2012). The CW plasma membrane interface is hypothesized as a key site for the stress signal perception where the interaction was studied between arabinogalactan proteins (AGPs) and receptor like kinases (Baluska et al., 2003). The production of hydrogen peroxide and downward redox signaling during the stress is an interesting aspect of CWPs (Spasojević and Pristov, 2010). The generation of reactive oxygen species (ROS) in response to CWP signaling (Barcelo and Laura, 2009) is an important and interesting phenomenon, because mitochondria and chloroplast are considered as the major players of ROS production (Voothuluru and Sharp, 2013). In response to abiotic stresses, the extracellular ROS accumulation is tightly regulated by the enzymes (Jaspers and Kangasjärvi, 2010) in cell membrane, which in turn are tightly bonded to the CW (Plieth, 2012). The speedy response of the CW (associated with the changes in its composition or structure) has led researchers to make a detailed study of the various functional proteins with an enzymatic activity within the CW. These include the CW formation, reorganization, loosening and carbohydrate metabolism (Brown et al., 2005; Gupta et al., 2005; Sasidharan et al., 2011; Xu et al., 2014).

Collectively, 2,170 CWPs have been identified on the basis of their distinct gene expression in various plants (San Clemente and Jamet, 2015). The glycoside hydrolases, lyses, esterases, and hydrolases come under the umbrella of proteins acting...
on polysaccharides (Jamet et al., 2008). The other class of oxidoreductases contains blue copper binding proteins, multicopper oxidases and peroxidases, while the proteases consist of Aspartate (Asp) proteases, ser carboxypeptidases, and cysteine (Cys) proteases. The oxidoreductases are an important class of enzymes that transfer OH group at critical physiological stages of plant development and affect the structure of the CW (Fry, 1998). Lipid transfer proteins are involved in lipid metabolism (Lev, 2010), and the AGPs in stress signaling (Shen et al., 2001). While, extensins (EXTs) and glycine rich proteins (GRPs) are the structural proteins. Some proteins, grouped as miscellaneous class like germin and germin like proteins, phosphatases and the phosphate inducible proteins, are still unclassified (Shahzad et al., 2013).

The in silico analyses showed 58 genes responsible for the regulation of proline based proteins in the CW of A. thaliana (Figure 3). The gene interaction and co-expression in the form of a wired network has been constructed for the cellular component and biological and molecular process. A significant variability has been observed in the degree of physical interactions, predicted interactions, co-expressions, genetic interactions, shared protein domains, and co-localization.

**Hydroxy-Proline Rich O-Glycoproteins (HRGPs)**

The HRGPs were recognized several decades earlier than the CWPs and marked as the complex macromolecules based on their chemistry and functionality (Wang et al., 2012). Based on glycosylation, HRGPs are categorized into three subclasses. These classes are hyper-glycosylated AGPs, moderately glycosylated EXTs and hyper PRPs (Tan et al., 2004). The HRGPs showed a specific multitude of functionalities. The cell signaling, defense, embryogenesis, development, reproduction, and expression are some of the recognized functions of AGPs (Seifert and Roberts, 2007). The EXTs are involved in the covalent scaffold and portrayed as the structural proteins of the CW (Cannon et al., 2008). The PRPs are the least developed proteins, and linked with the numerous biotic and abiotic stresses (Battaglia et al., 2007). The diversity of HRGPs further enhanced the addition of hybrid and chimeric proteins into the HRGPs family (Showalter et al., 2010). The gene mining of A. thaliana has revealed that 166 genes are encoding HRGPs, whereas 85 genes encode AGPs, 59 genes EXTs, 18 genes PRPs, and 4 genes hybrid proteins (Showalter et al., 2010). More than 50 genes were identified on the basis of their involvement in proline regulation in the CW for the 15 different functions. Even after more than 60 years of research, the detailed expression and functioning of HRGPs has not been clarified (Léonard et al., 2010). Several classes of the proteins share common function and sometimes a single class in the CW controls more than one function (Jamet et al., 2006). The AGPs are considered as the signaling proteoglycans but also sometime implicated to link the CW to the plasma lemma (Ellis et al., 2010). The EXTs play a vital role in the CW architecture (Lamport et al., 2011).

The HRGPs are evidently involved in growth, development, embryogenesis, apoptosis, and the CW architecture (Tan et al., 2012). The AGPs can be further divided into several classes, which may belong to the classical AGPs, non-classical AGPs, AG peptides, Lys-rich AGPs, Fasciclin-like AGPs (FLAs), and chimeric AGPs (Schultz et al., 2002). The AGPs attached to
the cell membranes (Gaspar et al., 2001), are encoded by 69 genes involved in the stress signaling and cellular processes (Ma and Zhao, 2010). The EXTs, under the pathogenic attack, were engaged in the peroxidase mediated cross-link to reduce its permeability (Cannon et al., 2008). To face stress in a better way (Ihsan et al., 2016), plant cells accumulate osmolytes (hydro-soluble carbohydrates) and proline to combat a water loss (Yamaguchi and Blumwald, 2005). Proline is synthesized from glutamate via a two-step oxido-reductase pathway involving the pyrroline-5-carboxylate synthase (P5CS) $\gamma$-glutamyl kinase ($\gamma$-GK), and glutamic-$\gamma$-semialdehyde dehydrogenase (GSA-DH; Chen et al., 2009). Increase in proline in response to stress is associated with the upregulation of its biosynthetic genes (Silva-Ortega et al., 2008). Thus, both proline levels and the expression of P5CS are useful markers for assessing the levels of stress acclimation through modifications in structure of the CW. It has been reported that overexpression of a novel feedback-desensitized $\Delta 1$-pyrroline-5-carboxylate synthetase increased proline accumulation in transgenic *Nicotiana plumbaginifolia* thereby conferring the salt tolerance in this plant (Ahmed et al., 2015).

The wired networking of genes, constructed through GENEVESTIGATOR, revealed a high extent of interaction and co-expression of clusters of genes controlling these classes of proteins (Figure 4). Differential interaction and co-expression has been observed between the genes for biological processes, molecular functions and cellular compartmentalization.

**Proline Rich Extensin like Proteins (PRExts)**

The PRExts are characterized partially in the superfamily of HRGPs and are implied in the assemblage of the CW and promotion of the cell growth and shape (Sasidharan et al., 2011). They have been studied extensively in previous decades (de Caestecker et al., 2000; Silva and Goring, 2002; Hsu et al., 2005; Bai et al., 2009). They formulate a highly known CWPs family. These are basic pectin interacting proteins containing Hyp O-glycosylated with short arabino-oligosaccharides. They can configure a helical structure named polyproline II, cross-linked through isodityrosine or di-isodityrosine (Choe and Cosgrove, 2010). In vitro scrutiny of atomic force microscopy has explored the pure form of *A. thaliana* “EXT3” constituting branchy structures, consistently cross-linked by the peroxidases (Geilfus et al., 2010). Likewise, threonine-rich hydroxyproline-rich glycoprotein (THRGP) found in maize were not cross-allied by the peroxidases. It was anticipated that the positive charged scaffolds produced by the assembly of EXTs in cell plates of the cell wall positively react with charged pectin through an ionic force. The presence of covalent interactions...
has also been proposed between EXTs and pectin. It has been found that a three dimensional covalent network was formed by the EXTs via Tyrosine (Tyr) linkages mediated by EXT (Cannon et al., 2008). The EXT monomers assemble in the CW in terminal zipper like organization through a cross linkage (Lamport et al., 2011). It is projected that an EXT associated with pectin further blossoms cell wall through an acid base reaction by forming a supra-molecular ionic structure. The EXTs constitute a three dimensional network of the glycoproteins with a pectin component of the CW (Voragen et al., 2009). The occurrence of the EXTs like chimeras and hybrid EXTs have also been confirmed in the CW (Showalter et al., 2010). Despite of the EXTs insolubility, their behavior has also been modified by the other domains of the proteins.

The characteristics articulated by the EXTs were just like the collagen cross-linked forming motifs (Lodish et al., 1999). However, contrary to collagen, the EXTs exhibit a plant specific post translational feature named O-glycosylation on the Ser-Hyp motifs. The experimental methodologies opted through molecular dynamics and homology modeling, recommended that classical EXTs would form a triple helical structure via the lateral staggered configuration and a Tyr cross-linking analogous to the collagen (Cannon et al., 2008). In the genome of A. thaliana, EXT is mentioned in the form of 59 members, like classical, chimeras and hybrids occupied by the different domains. No doubt, high number of EXT domains are residing in the CW but a little is known about their exact functionality and diversity during the plant developmental stages (Lamport et al., 2011). The analogous and repetitive sequences of proteins,
encoding of a large number of proteins in the same genome and simultaneous expression of the genes in the same tissue of plant are the different grounds that had created difficulty for us to perceive the exact biology of the EXTs.

The O-glycoproteins possessing EXT domains were finally integrated in the CW, put together by the different post translational modifications (PTMs), comprising processing of signal peptide by endoplasmic reticulum, proline hydroxylation, O-glycosylation, and Tyr cross linking in the CW (Nguema-Ona et al., 2014). In the past few years, research has revealed that several enzymes were involved in EXT fabrication pathways as a part of their PTMs. Even a small change in O-glycosylation status of EXTs affected the expansion of the polarized cell as observed by a drastic root hair appearance in mutants in response to the absence of glycosyltransferase (Velasquez et al., 2011). It has been reported that both types of the O-glycosylation located in the EXTs, were needed for the correct functionality of the EXTs during the root elongation. Somehow, it is not certain how the EXT monomer assembled into glycol-network and how the EXT pectin interactions are regulated during the nascent CW formation (Micheli, 2001). Through bioinformatics tools, we have found 21 genes encoding the EXTs like proteins in the CW that determined its structural architect at the molecular level and were expressed in different parts of the plant (Table 1).

**Arabinogalactan Proteins (AGPs)**

The AGPs are proteoglycans found in nearly all tissues and exudates of higher plants (Youl et al., 1998). These are 90% polysaccharides by composition and can be extracted in a low salt buffer and have been reported as non-structural part of the CW matrix (Fincher et al., 1983). These proteins belonged to the highly diversified hydroxyl proline-rich glycoproteins superfamily (Velasquez et al., 2011) in the plant kingdom. In Arabidopsis, the AGPs have been classified into 22 classes on the basis of their proteoglycan formation cohering with various developmental processes in plants (Showalter et al., 2010). However, the pectin and cellulose form the network structured by AGPs (Jia et al., 2015), which maintains the structural integrity of the CW. Moreover, the higher plant CWs constituted by cellulose micro-fibrils in
FIGURE 6 | A genome array map representing levels of expression of 10 selected genes at different developmental stages and a single selected gene for different anatomical parts in *Arabidopsis thaliana*. (A) Levels of expression at different developmental stages (from germination to senescence), which has been analyzed against different number of samples. (B) Expression level of a single selected gene AT1G54970 (PRP1) in 27 anatomical parts. Bars represent standard error at $P \leq 0.05$. 
glycoproteins, pectin and cellulose maintained the functional features, integrity and strength of the CW (Schwager et al., 2007; Ellis et al., 2010). Various studies have confirmed the prevalence of association between AGPs and pectin’s from plants tissue e.g., grapes, carrot and sugar beet. Co-localization of pectin’s and AGPs has been observed in the pollen tube (Mollet et al., 2006; Horiguchi et al., 2007; Mollet et al., 2008).
2002). When a plant CW was treated with the pectin degrading enzymes, an increase in the release of AGPs was observed, confirming an association between AGPs and pectin (Lamport et al., 2006). The interactions have also been reported between the AGPs and polysaccharides such as AGP-xylan complexes (Keegstra et al., 1973; Kwan and Morvan, 1995). An isoform of A. thaliana AGP (At3g45230) has been shown to be covalently linked with the pectins and hemicelluloses (Tan et al., 2012). Some AGPs function as polysaccharide plasticizers as they establish a cross linkage in the CW (Lamport et al., 2006).

A few AGPs were exposed to make the covalent interactions with the CW implying its role as a cross linker and pectin plasticizer, and to constitute complexes with the pectin and xylans (Tan et al., 2012). A complex arabinoxylan pectin arabinogalactan protein1 (APAP1) formed by the covalent interaction between A. thaliana AGP hemi cellulosic and pectic polysaccharide, has been reported to play some structural role in the CW (Tan et al., 2013). However, it is hypothesized that AGP31 established non-covalent cohesion in networks residing within the CW and could be extracted from the CW polysaccharides. The AGPs showed prominence in the covalent linkages with the pectin and hemicelluloses to restructure an APAP1 complex (Tan et al., 2013).

The AGPs determine plant growth, cell division, necrosis, zygotic division, and embryo formation (Majewska-Sawka and Nothnagel, 2000). They also play a role in somatic embryogenesis during embryonic development of plants (Businge and Egertsdotter, 2014). In Arabidopsis, the AGPs were located in the basal part of the suspensor (Hu et al., 2006). In Nicotiana, the expression of AGPs during the embryonic developmental stage was highly regulated (Geshi et al., 2013). Moreover, the potentiality of cellulose and pectin deposition in the CW was also hampered due to disruption in the AGPs functionality. Recent studies have focused on the structure biosynthesis and functionality of the AGPs enriched by a high percentage of sugars (Kitazawa et al., 2013). Thirteen genes encoding different types of AGPs with their roles are outlined in Table 2.

### Hybrid Proline Rich Proteins (HyPRPs)

The HyPRPs determine cell-type-specific wall structure during developmental phases and contribute in defensive mechanisms during the pathogenic infection. When treated with fungal elicitor, physical damage, and pathogen infection, the HyPRPs were rapidly insolubilized in the CW (Francisco and Tierney, 1990). They are a group of structural proteins formulating covalent cross linkages between the constituents of the CW (Showalter, 1993). They are further categorized on the basis of deoxyribonucleic acid (DNA) sequence similarity, continuity of motifs and domain organization (Fowler et al., 1999). The HyPRPs belonged to classical protein families with well-defined sequence but little is known about their systematic functioning. The CW based molecular mechanisms involved in evolution, ontogeny and functioning were purely based on theoretical interests albeit its major role was defined as a physical support to the cell. The HyPRPs are classified on the bases of different domains, proline rich N terminal repetitive, and hydrophobic C terminal domains (Neto et al., 2013). Previous data has revealed that the expression level and stimuli for HyPRPs differ significantly owing to plant developmental stage and environmental conditions. The blast analysis of Arabidopsis genome sequence revealed the involvement of 28 HyPRPs gene loci in the CW functions (Chardon et al., 2004). All chromosomes contained HPRPs genes but the higher number had been reported on second chromosome. The expression pattern of these genes is partially conserved between closely related paralogous genes. The exact role and compartmentalization of PRPs is still not well-understood compared to some better-characterized families. The PRPs are least glycosylated proteins that are extremely basic with the demonstration of specific repetitive motifs. Although there is no expressive evidence, still it is predicted that PRPs were cross linked by covalent bond within the CW (Tan et al., 2003). With the help of online tools, we have reported four genes controlling different kinds of PRPs in CW of A. thaliana, which are involved in different types of molecular processes in different localities (Table 3).

### GLYCINE RICH PROTEINS (GRPs)

The GRPs located within the CW of vascular tissues are regulated during the developmental stages of plants (Ye et al., 1991) by forming a third major group of CW proteins. The manifestation of many GRPs takes place under environmental stresses like water deficiency, high light, ABA, and pathogenic infestations. Although, it is presumed that GRPs were a part of the plant defense system, their mechanism of action is not yet known. It is possible that GRPs presenting other functional domains were necessary to determine how protein activity get affected under different conditions (Mangeon et al., 2010).

In plants, GRPs related genes are regulated during developmental stages and their expression varies in plant tissues (Yan et al., 2015). In different genera of plants, the expression of such genes is controlled by biotic and abiotic stresses (Ahmad et al., 2014; Alghabari et al., 2015, 2016; Ihsan et al., 2015; Yan et al., 2015). In plants, the categorization of GRPs is based on the semi-repetitive glycine rich motifs (Sachetto-Martins et al., 2000). According to a report, the French bean PvGRP1.8, a class 1 GRP, located in un-lignified primary CW, played a structural role in protoxylem through the CW buttressing (Ryser et al., 2004). Reverse genetics approaches have fortified the concept of the involvement of GRPs gene from Arabidopsis in the deposition of the secondary CW and maintenance of proto-xylem structure (Yokoyama et al., 2007).

Undoubtedly, the diversified structure, intonation, expression, prototype, and subcellular localization of GRPs are strongly witnessed for their prominent role and functionality in plants (Sachetto-Martins et al., 2000). Observations have disclosed the involvement and modulation of GRPs in the defense mechanism under pathogenic attack (de Souza Cândido et al., 2011). The NicCIGI gene was induced in turnip whose level was altered by tobacco virus, as shown by increased deposition of cellulose, which restricted the viral movement. This implicates structural roles of GRPs in conferring defense mechanisms.
### TABLE 1 | Proline-rich extensins genes in cell wall of *A. thaliana*†.

| Locus       | Gene ID | Biological process/Molecular function                              | Expressed/Located                                                                 | Description                                                                 | Some of related the references |
|-------------|---------|-------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------|--------------------------------|
| AT2G27380   | EPR1    | Component of CW                                                   | Micropylar endosperm                                                             | Extensin proline-rich 1                                                   | Penfield et al., 2006          |
| AT3G24550   | PERK1   | Protein phosphorylation and ATP binding                           | Carpel, cauline leaf and cotyledon                                              | Proline-rich extensin-like protein receptor kinase 1                       | Nemoto et al., 2011            |
| AT4G08410   |         | CW organization and CW structural constituent                     | Hypocotyl, plant embryo, root, sepal, and shoot apex                           | Proline-rich extensin-like protein                                          | Velasquez et al., 2011         |
| AT1G26250   | EXT18   | CW organization and CW structural constituent                     | Endomembrane system                                                             | Proline-rich extensin-like family protein                                   | Renaud et al., 2013            |
| AT5G06640   | EXT10   | CW organization and CW structural constituent                     | Hypocotyl, root, root hair cell, shoot apex, trichoblast, and vascular leaf     | Proline-rich extensin-like family protein                                   | Bruex et al., 2012             |
| AT2G43150   |         | CW organization and CW structural constituent                     | Carp, leaf structure, guard cell, hypocotyl, petal plant, shoot apex, stem, and vascular leaf | Proline-rich extensin-like family protein                                 | Sottosanto et al., 2004        |
| AT4G08370   |         | CW organization and CW structural constituent                     | Endomembrane system                                                             | Proline-rich extensin-like family protein                                   | Amengaud et al., 2004          |
| AT4G08400   |         | CW organization and CW structural constituent                     | Pollen                                                                         | Proline-rich extensin-like family protein                                   | −                              |
| AT1G26240   |         | CW organization and CW structural constituent                     | Root                                                                            | Proline-rich extensin-like family protein                                   | −                              |
| AT1G23720   |         | CW organization and CW structural constituent                     | Carp, hypocotyl, and root                                                       | Proline-rich extensin-like family protein                                   | Zhu et al., 2006               |
| AT3G54580   |         | CW organization and CW structural constituent                     | Pollen, pollen tube, root, root hair cell, and trichoblast                     | Proline-rich extensin-like family protein                                   | Bruex et al., 2012             |
| AT3G28550   |         | CW organization and CW structural constituent                     | Endomembrane system                                                             | Proline-rich extensin-like family protein                                   | −                              |
| AT5G35190   | EXT13   | CW organization and CW structural constituent                     | Root, root hair cell, and trichoblast                                           | Proline-rich extensin-like family protein                                   | Ma and Bohnert, 2007           |
| AT4G13390   | EXT12   | CW organization and CW structural constituent                     | Root hair cell and trichoblast                                                  | Proline-rich extensin-like family protein                                   | Diet et al., 2006              |
| AT2G24980   | EXT6    | CW organization and CW structural constituent                     | Root                                                                            | Proline-rich extensin-like family protein                                   | Velasquez et al., 2011         |
| AT5G06630   |         | CW organization and CW structural constituent                     | Collective leaf, hypocotyl, pollen, root, and vascular leaf                     | Proline-rich extensin-like family protein                                   | Dinneny et al., 2008           |
| AT1G20130   |         | Lipid metabolic process, lipase activity and CW structural constituent | Extracellular region                                                            | GDSL-motif esterase/acyltransferase/lipase                                  | Hanada et al., 2011            |
| AT5G38560   | PERK8   | Protein phosphorylation, ATP binding, and kinase activity         | Carp, cauline leaf, collective leaf structure, cotyledon, and cultured plant cell | Proline-rich extensin-like protein receptor kinase 8                       | Humphrey et al., 2014          |
| AT5G49080   | EXT11   | CW structural constituent                                         | Root hair cell, synergid and trichoblast                                        | Similar to proline-rich extensin-like family protein                       | Wuest et al., 2010             |
| AT3G54590   | HRGP1   | CW structural constituent                                         | Carp, cotyledon, flower, hypocotyl, and inflorescence meistem                   | Hydroxyproline-rich glycoprotein                                            | Wang et al., 2008              |
| AT4G08380   |         | −                                                                 | Synergid                                                                        | Proline-rich extensin-like family protein                                   | Wuest et al., 2010             |

† The information given in this table is based on TAIR database (Lamesch et al., 2012).
TABLE 2 | Arabinogalactan proteins genes in cell wall of A. thaliana†.

| Locus     | Gene ID | Biological process/Molecular function                          | Expresed in                                                                 | Description                                                                                   | Some of the related references |
|-----------|---------|---------------------------------------------------------------|------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|--------------------------------|
| AT5G55730 | FLA1    | Root and shoot system development                              | Vascular leaf, Carp, cauline leaf, collective leaf structure, guard cells, flower and inflorescence, cotyledon, flower, guard cell, hypocotyl, seed, root, and plant embryo | Fasciclin-like arabinogalactan protein 1                                                      | Sultana et al., 2015            |
| AT2G45470 | AGP8    | –                                                            | Carp, cauline leaf, leaf structure, guard cells, flower and inflorescence, cotyledon, flower, guard cell, hypocotyl, seed, root, and during different stages of plant embryo | Arabinogalactan protein 8                                                                  | Macmillan et al., 2010          |
| AT5G03170 | FLA11   | Plant-type secondary CW biogenesis                            | Carp, cauline leaf, collective leaf structure, guard cells, flower, and inflorescence | Fasciclin-like arabinogalactan protein 11                                                     | Macmillan et al., 2010          |
| AT5G14380 | AGP6    | Pollen tube growth and pollen tube viability                 | Carp, leaf structure, flower, petal, plant embryo and inflorescence          | Arabinogalactan protein 6                                                                    | Ja et al., 2015                 |
| AT3G01700 | AGP11   | Pollen tube growth                                           | Carp, leaf, flower, embryo, pollen, stamen, and pedicel                      | Loss of AGP11 function results in unfertile pollen tube due to defective growth.             | Costa et al., 2013              |
| AT2G24450 | FLA3    | N-terminal protein myristoylation                             | Carp, embroyo, pollen, flower, and stamen                                    | Fasciclin-like arabinogalactan protein 3                                                      | Johnson et al., 2011            |
| AT2G04780 | FLA7    | –                                                            | Carp, cotyledon, guard cell, inflorescence meristem, hypocotyl, shoot system, and leaf | Fasciclin-like arabinogalactan protein 7                                                      | Macmillan et al., 2010          |
| AT5G44130 | FLA13   | –                                                            | Seed, root, leaf, flower, and embryo                                         | Fasciclin-like arabinogalactan protein 13                                                     | Macmillan et al., 2010          |
| AT5G00490 | FLA12   | Secondary cell wall biogenesis                                | Vascular root, leaf, flower parts and peduncle                               | Fasciclin-like arabinogalactan protein 12                                                     | Macmillan et al., 2010          |
| AT5G10430 | AGP4/JAGGER | Synergid death                                         | Stamen, petal, root, leaf system, seed, and hypocotyl                        | Arabinogalactan protein 4                                                                    | Pereira et al., 2016            |
| AT5G07830 | GUS2    | Extracellular matrix organization and unidimensional cell growth | Carp, leaf, hypocotyl, root, seed, shoot, stem, and flower                  | A member of glycoside hydrolase family 79                                                    | Bayer et al., 2006              |
| AT2G15390 | FUT4    | CW organization and CW biogenesis                            | Carp, leaf, hypocotyl flower, guard cell, stem, stamen, and whole plant     | Fucosyltransferase 4                                                                         | Tryfona et al., 2014            |
| AT1G14080 | FUT6    | Fucosylation and cell wall biogenesis                         | Rowor, root, stem                                                            | Fucosyltransferase 6                                                                         | Liang et al., 2013              |

†The information given in this table is based on TAIR database (Lamesch et al., 2012).
### TABLE 3 | Proline rich proteins genes in cell wall of *A. thaliana*†.

| Locus      | Gene ID | Biological process/Molecular function                                     | Expresssed in/Located in                                                                 | Description                        | Some of the related references |
|------------|---------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------------------------------|---------------------------------|
| AT1G54970  | PRP1    | Trichoblast differentiation                                               | Root, root hair cell, trichoblast/CW, extracellular region                             | Proline-rich protein 1             | Bergonci et al., 2014           |
| AT2G21140  | PRP2    | CW organization                                                           | Leaf, stems, flowers, inflorescence meristem, stem, guard cell, petal/CW, extracellular region | Proline-rich protein 2             | Panjabi et al., 2008            |
| AT3G62680  | PRP3    | Cellular responses to auxin stimulus and calcium ion starvation, and trichoblast differentiation | Root hair cell, trichoblast/CW, extracellular region                                   | Proline-rich protein 3             | Bergonci et al., 2014           |
| AT4G38770  | PRP4    | Cysteine biosynthetic                                                     | Carpel, sepal, shoot apex, shoot system flower/CW, extracellular region               | Proline-rich protein 4             | Panjabi et al., 2008            |

† The information given in this table is based on TAIR database (Lamesch et al., 2012).

### TABLE 4 | Glycine rich protein genes in cell wall of *A. thaliana*†.

| Locus      | Gene ID | Biological process/Molecular function                                     | Expression in tissues                                                                 | Description                        | Some of the related references |
|------------|---------|---------------------------------------------------------------------------|----------------------------------------------------------------------------------------|------------------------------------|---------------------------------|
| AT4G39260  | GPR8    | Alternative mRNA splicing, Innate immune response, responses to ABA, salt stress, cold/Nucleic acid and nucleotide binding | Carpel, hypocotyl, leaf, juvenile vascular leaf, flower, fruit, guard cell, plant cell, plant embryo, seed and seedling developmental stages, and whole plant | Glycine-rich RNA-binding protein 8 | Leder et al., 2014              |
| AT4G18280  | –       | –                                                                         | Carpel, hypocotyl, leaf, juvenile vascular leaf, flower, fruit, guard cell, plant cell, plant embryo, shoot system, root and whole plant | Glycine-rich cell wall protein-related | Lan et al., 2007                |
| AT3G23830  | GPR4    | Response to cold/RNA and DNA binding                                       | Flower, guard cell, and cotyledon                                                     | Glycine-rich RNA-binding protein 4 | Han et al., 2013                |
| AT3G20470  | GPR5    | Response to ABA or salicylic acid stimulus, positive regulation of cell growth/CW structural constituent | Carpel, leaf, plant cell, Flower, fruit and leaf                                       | Glycine-rich protein 5             | Mangeon et al., 2010            |
| AT5G07530  | GRP17   | Lipid storage, pollen hydration, sexual reproduction/lipid binding        | Leaf, petal, pollen, flower, petal, sepal and stamen                                  | Glycine-rich protein 17            | Li-Beisson et al., 2010         |
| AT5G07510  | GRP14   | Lipid storage, sexual reproduction/Nutrient reservoir activity            | Collective leaf structure, flower, petal and sepal abundance it express in stems and with very low abundance it express in leaves | Glycine-rich protein 14            | Li-Beisson et al., 2010         |
| AT5G07520  | GRP18   | Lipid storage, sexual reproduction/Nutrient reservoir activity            | Collective leaf structure, flower, guard cell, petal and sepal                        | Glycine-rich protein 18            | Wellmer et al., 2004            |
| AT5G07550  | GRP19   | Lipid storage, sexual reproduction/lipid binding                          | Carpel, cauline leaf, collective leaf structure, flower, petal, sepal and stamen     | Glycine-rich protein 19            | Peiffer et al., 2008            |
| AT5G07540  | GRP16   | Lipid storage, sexual reproduction/lipid binding                          | Carpel, collective leaf structure, flower, petal, sepal and stamen                    | Glycine-rich protein 16            | Ehling et al., 2008             |
| AT2G15340  | –       | –                                                                         | Collective leaf structure, petal, flower, and pollen tube                            | Glycine-rich protein               | Wang et al., 2008               |
| AT1G48410  | AGO1    | Leaf proximal, distal pattern formation/miRNA and protein binding         | Carpel, leaf lamina, and inflorescence                                               | Glycine-rich protein               | Micot-Ponce et al., 2014        |
| AT3G15400  | ATA20   | Leaf proximal, distal pattern formation/miRNA and protein binding         | Carpel, cauline leaf, collective leaf structure, flower, petal, sepal and guard cell | Anther 20. Encodes a protein with novel repeat sequences and a glycine-rich domain, which has a 53% identity to GRP1, a petunia glycine-rich CW protein | Xu et al., 2010                 |

† The information given in this table is based on TAIR database (Lamesch et al., 2012).
TABLE 5 | Multiple function proline based genes in cell wall of A. thaliana†.

| Locus   | Gene ID | Biological process/Molecular function | Expressed in | Description                                                                 | Some of the related references |
|---------|---------|---------------------------------------|--------------|------------------------------------------------------------------------------|--------------------------------|
| AT5G14800 | P5C1    | Proline biosynthetic process/Pyrroline-5-carboxylate reductase activity | Carpels, flowers, guard cells, seed, shoot apex, root, stamens, pollen tube cell, and cotyledon | Delta 1-pyrroline-5-carboxylate reductase | Funck et al., 2012 |
| AT4G02330 | PME41   | CW modification/Pectin esterase activity | Carpels, flowers, guard cells, seed, shoot apex, root, stamens, pollen tube cell and cotyledon | Encodes a pectin methyl esterase that is sensitive to chilling stress and brassinosteroid regulation | Qu et al., 2011 |
| AT3G43270 |         | CW modification, pectin catabolic process/Pectin esterase activity | Carpels, flowers, guard cells, seed, shoot apex, root, stamens, pollen tube cell and cotyledon | Plant invertase/pectin methyl esterase inhibitor superfamily | Irshad et al., 2008 |
| AT2G19760 | PPFN1/PRF1 | Actin polymerization, cytoskeleton organization/Actin monomer binding | Carpels, flowers, guard cells, seed, shoot apex, root, stamens, pollen tube cell and cotyledon | Profilin 1 | Wang et al., 2009 |
| AT3G25500 | AFH1    | Actin cytoskeleton organization/Protein binding | Carpels, flowers, guard cells, seed, shoot apex, root, stamens, pollen tube cell and cotyledon | It is involved in signal-transduction cascade which results in rearrangement of the actin cytoskeleton | Rosero et al., 2016 |
| AT2G02990 | RNS1    | Anthocyanin-containing compound biosynthetic process, RNA binding and endoribonuclease activity | Flower, guard cell, carpel, collective leaf structure, petal, and embryo | Ribonuclease 1 is involved in wound induced signaling independent of JA | Nishimura et al., 2014 |
| AT5G14610 | APT1    | ATP binding | Carpels, flowers, guard cells, seed, shoot apex, root, stamens, pollen tube cell and cotyledon | DEAD box RNA helicase family protein | Spencer et al., 2007 |
| AT3G22070 | –       | – | Flower, guard cell, inflorescence meristem, root, seed, shoot apex | Proline-rich family like protein | – |

†The information given in this table is based on TAIR database (Lamesch et al., 2012).

in plants (Ueki and Citovsky, 2002). The GRPs constitute almost 70% glycine (Kar et al., 2012). Analysis done by immunocytochemistry has revealed their direct alliance with proto-xylem, where they play a prominent role in repair and stretching phase (Sachetto-Martins et al., 2000). It is perceived that the continuity of glycine rich domains produced beta pleated hydrophobic structure. An in vitro cross-linking experiment in the presence of peroxidases has explored the configuration of networks in Tyr-containing GRPs. Nonetheless, there is further need to do experimentation to generate data to support the characterization of intra and inter molecular networks involving GRPs.

The GRPs are presumed to be involved in promoting expression of genes in plants, exemplified through the involvement of RNA binding GRP gene AtCSG2 and their regulation during flower development (Sachetto-Martins et al., 2000). The plants in which AtCSG2 was silenced due to biotic or abiotic stress showed premature flowering with reduced stamens and abnormal embryo development (Fusaro et al., 2007). The GRPs yet isolated from plants are categorized as CW-GRPs, RNA-GRPs, and cytokeratin like GRPs (Sharma et al., 2012). Analysis conducted through bioinformatics tools has explored 12 genes controlling different types of GRPs in the CW of A. thaliana. These genes also perform salient molecular functions in different kinds of cells and plant parts (Table 4). The study has also revealed eight genes, which could not be categorized to any kind of CWP and the functions of these genes are indicated in Table 5.

GENE CO-EXPRESSION FUNCTIONALITY

In A. thaliana, 2,700 proteins express 6,200 highly reliable interactions. The interactive maps provided a dynamic approach in better understanding of the plant biological systems and a base for future crop improvement (Braun et al., 2011). The exploitation of co-expression networks in Arabidopsis provides a dimension to mine genes involved in the synthesis of CW and to unravel the structural hierarchy of Arabidopsis in systematic progression (Obayashi and Kinoshita, 2009). Here, we have made queries through PubMed to understand the genes expression and co-expression in a wired way in the CW through different kinds of structural proteins. Through bioinformatics tools, 58 genes involved in proline based CW regulation were found. The established wired networks showed the genes co-expression, and interaction in structural components, biological processes and molecular functions by regulating the synthesis of proline based CW proteins. In regulation of biological processes, these genes have shown physical interaction 55.7%, co-expression 15.6%, genetic interaction 6.9%, shared proteins domains 3.6%, and co-localization 0.6% (Figure 3). However, in determining cellular components, these genes have revealed physical interaction 7.4%, co-expression 55.9%, genetic interaction 1.1%, shared proteins domains 2.9%, and co-localization 1.8%. Moreover, these proteins helped in signal transduction by regulating the molecular functions for which physical interaction 39.0%, co-expression 11.8%, genetic interaction 3.3%, shared proteins domains 14.6%, and co-localization 0.4% were calculated.
Similarly, gene networking and interaction, based on biological process, molecular process and cellular component for protein rich protein extensins, GRPs, arabinogalactan proteins, and PRPs indicated the genes co-expression and interaction even when they were considered separately for a particular family of proteins (Figure 4). These wired networks as a whole, are the clusters of genes repertoire, interacting and co-expressing for different kinds of proteins present in the CW. However, out of this treasury of genes, we mined the genes interacting for a particular class of proteins. Therefore, in this complete wired network, we have showed genes, which are interacting for a specific family of proteins as dark (black) spots. However, light spots represented those genes whose interactions were not considered (Figure 4).

The immense knowledge as an outcome of genome sequencing paves the way to understand the working philosophy of genes in an integrated way on genome sequencing, expression analysis and protein interaction. The transcriptional coordination has been estimated using PCC. By using this method, co-expression relationships between many genes can be estimated, and visualized as a network in which nodes indicate genes whereas connection between nodes represents the transcriptional coordination of genes (Aoki et al., 2007). The PCC method sometimes becomes defective when some biological processes are strongly transcriptionally co-regulated, while other processes are not. In addition to this, a lower value of PCC results in excessively large gene clusters, possessing thousands of genes (Mao et al., 2009).

The PCC for 50 proline based CW regulating selected genes presented a positive and negative co-expression of +0.969 and −0.827, respectively (Figure 7). Hierarchical clustering of genes based on PCC indicated the co-expression of some genes with same intensity at particular developmental stage with altered expression level changing in the developmental stage (Figure 8). The genes that showed co-expression also represented a high degree of functional correlation. Co-expressions studies of genes can be used to identify other genes. For example, in cellulose synthesis, the co-expression approach can be used to identify the genes involved in the synthesis of hemicellulose (Cocuron et al., 2007). Many genes that are transcriptionally associated with the synthesis of the CW have been already studied (Ruprecht et al., 2011). The genetic redundancy needs mutant combinations or knocks down approaches that will focus upon several homologous genes to generate informative phenotypes. In addition to this, detailed comparative transcriptional studies are still required to mine candidate genes for the CW synthesis.

The co-expression analysis gives one possible caveat of “false positives,” which means some genes are co-expressed by chance rather than being functionally related. However, it has been reported that co-expression relationships are often conserved across species (Obayashi and Kinoshita, 2009). Hence, co-expression analysis across species can improve the reliance of co-expression based functional annotation.

Through computational methodologies, we have generated figures highlighting the expression of genes at different plant specific stages. The module-based predictions provide an approach to formulate hypothesis for functionally unknown genes (1,701) in Arabidopsis and other plant species. It also provides a new imminent into the conservation of co-expression and co-regulation (Heyndrickx et al., 2014). Through proteins architecture studies of the CW, we have identified several genes directly and indirectly involved in proteome manufacturing (Yang et al., 2011). In response to heat stress, P5CR launches...
its oxido-reductase activity by producing pyrroline-5-carboxylate reductase enzyme at the vicinity of the cytoplasm and CW. Under the conditions of biotic and abiotic stresses, the gene express itself in CW compartment by enhancing proline transport and increasing sensitivity against pathogenic stimuli (Bosch et al., 2011). Hence, modifications in CW proteins and proline transport are an indicator of regulation of genes expression under biotic stresses.

For co-expression studies, the bioinformatics tools have been focused on the model plant Arabidopsis by including the major bulk of publicly available microarray datasets. The candidate genes forming the foundation of the existing A. thaliana CW regulatory network, have been identified by gene expression profiling (Handakumbura and Hazen, 2012). Genes with similar functionality and overlapping effects, such as expression and regulation of floral developmental and defense related genes in response to biotic stress (Ahmad et al., 2013, 2014), can also be coordinated as indicated by global transcript analysis based upon publicly available microarray datasets. Certainly, through co-expression analysis in A. thaliana, many transcriptionally coordinated genes involved in the formation of CW proteins, cellulose, hemicelluloses and lignin have been identified. To facilitate this co-expression analysis, several helpful web based tools have been developed for the researchers to investigate transcriptional co-orderings as well as to mine the candidate genes involved in the CW integrity. In addition, several tools paved the foundation to make comparative transcriptional analysis across many species, which will potentially increase predictive power about gene functionality.

AUTHOR CONTRIBUTIONS

ZA, JNA, and MI came up with the ideas and reviewed all the literature; MI, SJNA, ZS, and HR took part in writing the manuscript. IA, JNA, and AMB reviewed, critically analyzed and edited the manuscript. All authors discussed and commented on the manuscript.

ACKNOWLEDGMENTS

AMB, JNA, SJNA, and IA acknowledge the financial support from PAK 3004 Framework for Pak-Norway Institutional Co-operation Programme.

REFERENCES

Ahmad, J. N., Pracros, P., Garcia, C., Teysnier, E., Renaudin, J., Hernould, M., et al. (2013). Effects of stolbur phytoplasma infection on DNA methylation processes in tomato plants. Plant Pathol. 62, 205–216. doi: 10.1111/j.1365-3059.2012.02605.x

Ahmad, J. N., Renaudin, J., and Eveillard, S. (2014). Expression of defense genes in stolbur phytoplasma infected tomatoes, and effect of defense stimulators on disease development. Eur. J. Plant Pathol. 139, 39–51. doi: 10.1007/s10658-013-0361-x

Ahmed, A. A. M., Roosens, N., Dewaele, E., Jacobs, M., and Angenon, G. (2015). Overexpression of a novel feedback-desensitized Δ1-pyrroline-5-carboxylate synthetase increases proline accumulation and confers salt tolerance in transgenic Nicotiana plumbaginifolia. Plant Cell Tissue Organ Cult. 122, 383–393. doi: 10.1007/s11240-015-0776-5

Ahuja, I., de Vos, R. C. H., Rohloff, I., Sroopen, G. M., Halle, K. K., Ahmad, S. J. N., et al. (2016). Arabidopsis myrosinases link the glucosinolate–myrosinase system and the cuticle. Sci. Rep. 6:38990. doi: 10.1038/srep38990

Albenne, C., Canut, H., and Jamet, E. (2013). Plant cell wall proteomics: the leadership of Arabidopsis thaliana. Front. Plant Sci. 4:111. doi: 10.3389/fpls.2013.00111

Alghabari, F., Ihsan, M. Z., Hussain, S., Aishia, G., and Daur, I. (2015). Effect of Rht alleles on wheat grain yield and quality under high temperature and drought stress during booting and anthesis. Environ. Sci. Pollut. Res. 22, 15506–15515. doi: 10.1007/s11356-015-4274-2

Alghabari, F., Ihsan, M. Z., Khalqi, A., Hussain, S., Daur, I., Fahad, S., et al. (2016). Gibberellin-sensitive Rht alleles confer tolerance to heat and drought stresses in wheat at booting stage. J. Cereal Sci. 70, 72–78. doi: 10.1016/j.jcs.2016.05.016

Aoki, K., Perlman, M., Lim, J.-M., Cantu, R., Wells, L., and Tiemeyer, M. (2007). Dynamic developmental elaboration of N-linked glycan complexity in the Drosophila melanogaster embryo. J. Biol. Chem. 282, 9127–9142. doi: 10.1074/jbc.M606671200

Armengaud, P., Breitling, R., and Atmamn, A. (2004). The potassium-dependent transcriptome of Arabidopsis reveals a prominent role of jasmonic acid in nutrient signaling. Plant Physiol. 136, 2536–2576. doi: 10.1104/pp.104.046482

Bai, L., Zhou, Y., and Song, C.-P. (2009). Arabidopsis proline-rich extensin-like receptor kinase 4 modulates the early event toward abscisic acid response in root tip growth. Plant Signal. Behav. 4, 1075–1077. doi: 10.4161/psb.4.11.9739

Baluška, F., Šamaj, J., Wojtaszek, P., Volkmann, D., and Menzel, D. (2003). Cytoskeleton–plasma membrane–cell wall continuum in plants. Emerging links revisited. Plant Physiol. 133, 482–491. doi: 10.1104/pp.103.027250

Barceló, A. R., and Laura, V. R. G. (2009). "Reactive oxygen species in plant cell walls," in Reactive Oxygen Species in Plant Signaling, eds A. L. Rio and A. Pupo (Berlin; Heidelberg: Springer), 73–93.

Battaglia, M., Solórzano, R. M., Hernández, M., Cuéllar-Ortiz, S., García-Gómez, R., Márquez, J., et al. (2007). Proline-rich cell wall proteins accumulate in growing regions and phloem tissue in response to water deficit in common bean seedlings. Planta 225, 1121–1133. doi: 10.1007/s00425-006-0423-9

Bayer, E. M., Bottrill, A. R., Walshaw, J., Vigouroux, M., Naldrett, M. J., Thomas, C. L., et al. (2006). Arabidopsis cell wall proteome defined using multidimensional protein identification technology. Proteomics 6, 301–311. doi: 10.1002/pmic.200500046

Bellincampi, D., Cervone, F., and Lionetti, V. (2014). Plant cell wall dynamics and wall-related susceptibility in plant-pathogen interactions. Front. Plant Sci. 5:228. doi: 10.3389/fpls.2014.00228

Bergonci, T., Ribeiro, B., Cecchiato, P. H. O., Guererro-Abad, J. C., Silva-Filho, M. C., and Moura, D. S. (2014). Arabidopsis thaliana RALF1 opposes brassinosteroid effects on root cell elongation and lateral root formation. J. Exp. Bot. 65, 2219–2230. doi: 10.1093/jxb/eru099

Beyer, A., Bandyopadhyay, S., and Ideker, T. (2007). Integrating physical and genetic maps: from genomes to interaction networks. Nat. Rev. Genet. 8, 699–710. doi: 10.1038/nrg2144

Boron, A. K., Van Orden, J., Nektarios Markakis, M., Mouille, G., Adriaensen, D., Verbelen, J.-P., et al. (2014). Proline-rich protein-like PRPL1 controls elongation of root hairs in Arabidopsis thaliana. J. Exp. Bot. 65, 5485–5495. doi: 10.1093/jxb/eru308

Bosch, M., Mayer, C.-D., Cookson, A., and Donnison, I. S. (2011). Identification of genes involved in cell wall biogenesis in grasses by differential gene expression profiling of elongating and non-elongating maize internodes. J. Exp. Bot. 62, 3545–3561. doi: 10.1093/jxb/err045

Boudart, G., Jamet, E., Rossignol, M., Lafitte, C., Borderies, G., Jauneau, A., et al. (2005). Cell wall proteins in apoplastic fluids of Arabidopsis thaliana rosettes: identification by mass spectrometry and bioinformatics. Proteomics 5, 212–221. doi: 10.1002/pmic.200400882
Braun, J. E., Huntzinger, E., Fauser, M., and Izaurralde, E. (2011). GW182 proteins directly recruit cytoplasmic deadenylase complexes to miRNA targets. Mol. Cell 44, 120–133. doi: 10.1016/j.molcel.2011.09.007

Brown, D. M., Zee, L. A. H., Ellis, J., Goodacre, R., and Turner, S. R. (2005). Identification of novel genes in Arabidopsis involved in secondary cell wall formation using expression profiling and reverse genetics. Plant Cell 17, 2281–2295. doi: 10.1105/tpc.105.031542

Bruex, A., Kainkaryam, R., Mieckowski, Y., Kang, Y. H., Bernhardt, C., Xiu, Y., et al. (2012). A gene regulatory network for root epidermis cell differentiation in Arabidopsis. PLoS Genet. 8:e1002446. doi: 10.1371/journal.pgen.1002446

Businge, E., and Egertsdottter, U. (2014). A possible biochemical basis for fructose-induced inhibition of embryo development in Norway spruce (Picea abies). Tree Physiol. 34, 657–669. doi: 10.1093/treephys/tpu053

Cannon, M. C., Termeus, K., Hall, Q., Tan, L., Wang, Y., Wegenhart, B. L., et al. (2008). Self-assembly of the plant cell wall requires an extensin scaffold. Proc. Natl. Acad. Sci. U.S.A. 105, 2225–2231. doi: 10.1073/pnas.0711980105

Chardon, F., Viron, B., Moreau, L., Falque, M., Joets, J., Decousset, L., et al. (2004). Genetic architecture of flowering time in maize as inferred from quantitative trait loci meta-analysis and synteny conservation with the rice genome. Genetics 168, 2169–2185. doi: 10.1534/genetics.104.032375

Chen, J. B., Wang, S. M., Jing, R. L., and Mao, X. G. (2009). Cloning the PpVPS5 gene from common bean (Phaseolus vulgaris) and its expression patterns under abiotic stresses. J. Plant Physiol. 166, 12–19. doi: 10.1016/j.jplph.2008.02.010

Choe, H.-T., and Cosgrove, D. J. (2010). “Expansins as agents in hormone action,” in Plant hormones: Biosynthesis, Signal Transduction, Action! ed P. J. Davies (Dordrecht: Springer). 262–281.

Cocuron, J.-C., Lerouxel, O., Drakakaki, G., Alonso, A. P., Liepman, A. H., Croissant, D., et al. (2013). A galactosyltransferase acting on arabinogalactan protein glycans is essential for embryo development in Arabidopsis. Plant J. 76, 128–137. doi: 10.1111/tjp.12281

Gupta, A. K., and Kaur, N. (2005). Sugar signalling and gene expression in relation to carbohydrate metabolism under abiotic stresses in plants. J. Biosci. 30, 761–776. doi: 10.1007/BF02703574

Han, J. H., Jung, Y. J., Lee, H.-J., Jung, H. S., Lee, K. O., and Kang, H. (2013). The RNA chaperone and protein chaperone activity of Arabidopsis glycine-rich RNA-binding protein 4 and 7 is determined by the propensity for the formation of high molecular weight complexes. J. Proteome Res. 12, 449–455. doi: 10.1021/jr300930-13950-3

Hanada, K., Sawada, Y., Kuromori, T., Klausnitzer, R., Saito, K., Toyoda, T., et al. (2011). Functional compensation of primary and secondary metabolites by duplicate genes in Arabidopsis thaliana. Mol. Biol. Evol. 28, 377–382. doi: 10.1093/molbev/msq204

Handakumbura, P. P., and Hazen, S. P. (2012). Transcriptional regulation of grass secondary cell wall biosynthesis: playing catch-up with Arabidopsis thaliana. Front. Plant Sci. 3:74. doi: 10.3389/fpls.2012.00074

Heyndrickx, K. S., De Velde, J. V., Wang, C., Weigel, D., and Vandevoorde, K. (2014). A functional and evolutionary perspective on transcription factor binding in Arabidopsis thaliana. Plant Cell 26, 3894–3910. doi: 10.1105/tpc.114.130591

Hsu, H.-C., Lee, Y.-L., Cheng, T.-S., Howung, S.-L., Chang, I.-K., Lu, P.-J., et al. (2005). Characterization of two non-testis-specific CAYBYR variants that bind to GSK3β with a proline-rich extension-like domain. Biochem. Biophys. Res. Commun. 329, 1108–1117. doi: 10.1016/j.bbrc.2005.02.089

Hu, Y., Qin, Y., and Zhao, J. (2006). Localization of an arabinogalactan protein epitope and the effects of Yariv phenylglycoside during zygotic embryo development of Arabidopsis thaliana. Plant Physiol. 142, 21–31. doi: 10.1104/pp.106.070979

Humphrey, T. V., Haasen, K., and Illakka-Brydges, M. G., Sun, H., Zayed, Y., Indriolo, E., et al. (2014). PERK-PIP3–KCIP1 signalling negatively regulates root growth in Arabidopsis thaliana. J. Exp. Bot. 66, 71–83. doi: 10.1093/jxb/eru390

Ihsan, M. Z., El-Nakhlayy, F. S., and Ismail, S. M. (2015). Water use efficiency, growth and yield of wheat cultivated under competition with Setaria. Planta Daninha 33, 679–687. doi: 10.1590/S0100-83852015000400006

Ihsan, M. Z., El-Nakhlayy, F. S., Ismail, S. M., Fahad, S., and Daur, I. (2016). Wheat phenological development and growth studies as affected by drought and late season high temperature stress under arid environment. Front. Plant Sci. 7:795. doi: 10.3389/fpls.2016.00795

Irishad, M., Canut, H., Borderies, G., Pont-Lezica, R., and Jamet, E. (2008). A new picture of cell wall protein dynamics in elongating cells of Arabidopsis thaliana: confirmed actors and newcomers. BMC Plant Biol. 8:94. doi: 10.1186/1471-2229-8-94

Jamet, E., Albene, C., Boudart, G., Irisch, M., Canut, H., and Pont-Lezica, R. (2008). Recent advances in plant cell wall proteomics. Proteomics 8, 983–908. doi: 10.1002/pmic.20070938

Jamet, E., Canut, H., Boudart, G., and Pont-Lezica, R. F. (2006). Cell wall proteins: a new insight through proteomics. Trends Plant Sci. 11, 33–39. doi: 10.1016/j.tplants.2005.11.006

Jaspers, P., and Kangasjärvi, J. (2010). Reactive oxygen species in abiotic stress signal transduction. Physiol. Plant. 138, 405–413. doi: 10.1111/j.1399-3054.2009.01321.x

Jia, Q.-S., Zhu, J., Xu, X.-F., Lou, Y., Zhang, Z.-L., Zhang, Z.-P., et al. (2015). Arabidopsis AT-hook protein TPK2 positively regulates the expression...
of arabinoogalactan proteins for nexine formation. Mol. Plant 8, 251–260. doi: 10.1016/j.molp.2014.10.001
Johnson, K. L., Kibble, N. A. J., Back, A., and Schultz, C. J. (2011). A fasciclin-like arabinoogalactan-protein (fla) mutant of Arabidopsis thaliana shows defects in shoot regeneration. PLoS ONE 6:e25154. doi: 10.1371/journal.pone.0025154
Kacperska, A. (2004). Sensor types in signal transduction pathways in plant cells responding to abiotic stressors: do they depend on stress intensity? Physiol. Plant. 122, 159–168. doi: 10.1111/j.0031-9317.2004.00388.x
Kar, B., Nayak, S., and Joshi, R. K. (2012). Classification and comparative analysis of the extrensin superfamily in primary cell wall architecture. Mol. Plant 51, 188–197. doi: 10.1104/pp.11.1.188
Kitazawa, K., Tryfona, T., Yoshimi, Y., Hayashi, Y., Kawauschi, S., Antonov, L., et al. (2013). β-galactosyl yariv reagent binds to the β-1,3-galactan of arabinoogalactan proteins. Plant Physiol. 161, 1117–1126. doi: 10.1104/pp.11.2.11722
Kwan, J. S., and Morvan, H. (1995). Characterization of extracellular (β1,4)-xylan backbone O-substituted by arabinoogalactan type II in a plant cell suspension. Carbohyd. Polym. 26, 99–107. doi: 10.1016/0144-8617(94)00099-E
Lamesh, P., Berardini, T. Z., Li, D., Swarbreck, D., Wilks, C., Sasidharan, R., et al. (2012). The Arabidopsis Information Resource (TAIR): improved gene annotation and new tools. Nucleic Acids Res. 40, D1202–D1210. doi: 10.1093/nar/gdr1090
Lampert, D. T. A., Kieliszewski, M. J., and Showalter, A. M. (2006). Salt stress upregulates periplasmic arabinogalactan proteins: using salt stress to classify cell wall architectures. Front. Plant Sci. 143, 1314–1326. doi: 10.1016/j.toso.2009.05.004
Michel, F. (2001). Pectin methyltransferases: cell wall enzymes with important roles in plant physiology. Trends Plant Sci. 6, 414–419. doi: 10.1016/S1360-1385(01)02045-3
Micol-Ponce, R., Aguiler, V., and Ponce, M. R. (2014). A genetic screen for suppressors of a hypomorphic allele of Arabidopsis ARGAONE1. Sci. Rep. 4:5533. doi: 10.1038/srep05533
Mollèt, J.-C., Kim, S., Jauh, G.-Y., and Lord, M. E. (2002). Arabinoogalactan proteins, pollen tube growth, and the reversible effects of Yariv phenylglycoside. Protoplasma 219, 89–98. doi: 10.1007/s007090200009
Moliner, K., Neto, T., Takahashi, H., Nozawa, A., Seki, S., Shinoki, K., et al. (2011). Autophosphorylation profiling of Arabidopsis kinases using the cell-free system. Phytochemistry 72, 1134–1144. doi: 10.1016/j.phytochem.2011.02.029
Neto, L. B., De Oliveira, R. R., Wiebe-Strohm, B., Bencke, M., Weber, R. L. M., Cabreira, C., et al. (2013). Identification of the soybean HyPRP family and specific gene response to Asian soybean rust disease. Genet. Mol. Biol. 36, 214–224. doi: 10.1590/S1471-24472013000500011
Ngueuma-Ona, E., Vicré-Gibouin, M., Gotté, M., Plancot, B., Lerouge, P., Bador, M., et al. (2014). Cell wall O-glycoproteins and N-glycoproteins: biosynthesis and some functional aspects. Front. Plant Sci. 5:499. doi: 10.3389/fpls.2014.00499
Nishimura, E., Jumyo, S., Arai, N., Kume, K., Nishikawa, J.-I., et al. (2010). Structural and functional characteristics of S-like ribonucleases from carnivorous plants. Planta 240, 147–159. doi: 10.1007/s00425-014-2072-8
Northcote, D. H., Goulding, K. J., and Horne, R. W. (1960). The chemical composition and structure of the cell wall of Hydrodictyon africanum Yaman. Biochem. J. 77, 503–508. doi: 10.1042/bj0770503
Obayashi, T., and Kinoshita, K. (2009). Rank of correlation coefficient as a comparable measure for biological significance of gene coexpression. DNA Res. 16, 249–260. doi: 10.1093/dnares/dsp016
Oikawa, A., Joshi, H. J., Rennie, E. A., Ebert, B., Manisier, C., Heazlewood, J. L., et al. (2010). An integrative approach to the identification of Arabidopsis and rice genes involved in xylan and secondary wall development. PLoS ONE 5:e15481. doi: 10.1371/journal.pone.0015481
Panjabi, P., Jagannath, A., Bisht, N. C., Padmaja, K. L., Sharma, S., Gupta, V., et al. (2008). Comparative mapping of Brassica juncea and Arabidopsis thaliana using Intron polymorphism (IP) markers: homoeologous relationships, diversification and evolution of the A, B and C Brassica genomes. BMC Genomics 9:113. doi: 10.1186/1471-2164-9-113
Peifer, J. J., Kaushik, S., Sakai, H., Arteaga-Vazquez, M., Sanchez-Leon, N., Ghazali, H., et al. (2008). A spatial dissection of the Arabidopsis floral transcriptome by MPSS. BMC Plant Biol. 8:43. doi: 10.1186/1471-2229-8-43
Penfield, S., Li, Y., Gilday, A. D., Graham, S., and Graham, I. A. (2006). Arabidopsis ABAP INSENSITIVE4 regulates lipid mobilization in the embryo and reveals repression of seed germination by the endosperm. Plant Cell 18, 1887–1899. doi: 10.1105/tpc.106.041277
Pereira, A. M., Nobre, M. S., Pinto, S. C., Lopes, A. L., Costa, M. L., Masiero, S., et al. (2016). “Love Is Strong, and You’re so Sweet”: JAGGER is essential for persistent synergistic degradation and putrefyube block in Arabidopsis thaliana. Mol. Plant 9, 601–614. doi: 10.1093/mp/2016.1.00102
Plith, C. (2012). Aporplastic calcium executes a shut-down function on plant peroxidases: a hypothesis. Plant Signal. Behav. 7, 678–681. doi: 10.4161/psh.20007
Qu, T., Liu, R., Wang, W., An, L., Chen, T., Liu, G., et al. (2011). Brassinosteroids regulate pectin methylesterase activity and AtPME41 expression in Arabidopsis under chilling stress. Cryobiology 63, 111–117. doi: 10.1016/j.cryobiol.2011.07.003

Renault, H., El Amrani, A., Berger, A., Mouillé, G., Soubigou-Taconnat, L., Boucheau, A., et al. (2013). γ-Aminobutyric acid transaminase deficiency impairs central carbon metabolism and leads to cell wall defects during salt stress in Arabidopsis roots. Plant Cell Environ. 36, 1009–1018. doi: 10.1111/pce.12033

Rosero, A., Oulehlová, D., Stillerová, L., Schiebertová, P., Grunt, M., Žáský, V., and Červková, F. (2016). Arabidopsis FHII form affects cotyledon pavement cell shape by modulating cytokinesis dynamics. Plant Cell Physiol. 57, 488–504. doi: 10.1093/pcp/pcv209

Ruprecht, C. R., Krarup, A., Reynell, L., Mann, A. M., Brandenberg, O. F., Berlinger, L., et al. (2011). MPER-specific antibodies induce gp120 shedding and irreversibly neutralize HIV-1. J. Exp. Med. 208, 439–454. doi: 10.1084/jem.20101907

Ryser, U., Schorderet, M., Guyot, R., and Keller, B. (2004). A new structural element containing glycine-rich proteins and rhhamnogalacturonan I in the protoplast of seed plants. J. Cell Sci. 117, 1179–1190. doi: 10.1242/jcs.009966

Sachetto-Martins, G., Franco, L. O., and De Oliveira, D. E. (2000). Plant glycin-rich proteins: a family or just proteins with a common motif? Biochim. Biophys. Acta Gen. Struct. Express. 1492, 1–14. doi: 10.1016/S0167-4781(00)00864-7

San Clemente, H., and Jamet, E. (2015). WallProtDB, a database resource for plant cell wall proteomics. Plant Methods 11, 1–7. doi: 10.1186/s13007-015-0045-y

Sasidharan, R., Voesenek, L. A. C. J., and Pierik, R. (2011). Cell wall modifying proteins mediate plant acclimatization to biotic and abiotic stresses. Crit. Rev. Plant Sci. 30, 548–562. doi: 10.1080/07352689.2011.615706

Schultz, C. J., Rumsewicz, M. P., Johnson, K. L., Jones, B. J., Gaspar, Y. M., and Bacic, A. (2002). Using genomic resources to guide research directions. The arabidopsis protein gene family as a test case. Plant Physiol. 129, 1448–1463. doi: 10.1104/pp.003449

Schwager, K. M., Calderon-Villalobos, L. I. A., Dohmann, E. M. N., Willige, B. C., Knierer, S., Nill, C., et al. (2007). Characterization of the VIER F-BOX PROTEIN genes from Arabidopsis reveals their Importance for plant growth and development. Plant Cell 19, 1163–1178. doi: 10.1105/tpc.105.040675

Seifert, G. J., and Roberts, K. (2007). The biology of arabidopsis proteins. Annu. Rev. Plant Biol. 58, 137–161. doi: 10.1146/annurev.arplant.58.032806.103801

Shahzad, A., Muhammad, I., Muhammad, A., Hirani, A. H., and Goyal, A. (2013). Growing wheat on saline lands: can a dream come true? Aust. J. Crop Sci. 7, 515–524.

Shavvery, P., Iba, A. B., Dubey, R. S., and Pessarakli, M. (2012). Reactive oxygen species, oxidative damage, and antioxidative defense mechanism in plants under stressful conditions. J. Bot. 2012,217037. doi: 10.1155/2012/217037

Shen, W., Gómez-Cadenas, A., Routly, E. L., Ho, T.-H. D., Simmonds, J. J., and Cvrčková, F. (2016). The systemic movement of a tobanovirus is specific to the apical region of growth maintenance. J. Integr. Plant Biol. 58, 113–121. doi: 10.1111/jipb.12033

Stehle, S., et al. (2011). O-glycosylated cell wall proteins are essential in root hair growth. Science 332, 1401–1403. doi: 10.1126/science.1206657

Verica, J. A., and He, Z. (2002). The cell wall-associated kinase (WAK) and WAK-like kinase gene family. Plant Physiol. 129, 455–459. doi: 10.1104/pp.011028

Vinocur, B., and Altman, A. (2005). Recent advances in engineering plant tolerance to abiotic stress: achievements and limitations. Crit. Rev. Bot. 21, 123–138. doi: 10.1111/j.1744-7909.2005.00212.x

Voolhuur, P., and Sharp, R. E. (2013). Aporplastic hydrogen peroxide in the growth zone of the maize primary root under water stress. I. Increased levels are specific to the apical region of growth maintenance. J. Exp. Bot. 64, 1223–1233. doi: 10.1093/jxb/erx277

Voragen, A. G. J., Coenen, G.-J., Verhoef, R. P., and Schols, H. A. (2009). Pectin–cellulose interactions in Arabidopsis primary cell wall from two-dimensional magic-angle-spinning solid-state nuclear magnetic resonance. Biochemistry 51, 9846–9856. doi: 10.1021/bi9015532

Wang, T., Zhang, W.-Z., Song, L.-F., Zou, J.-J., Su, Z., and Wu, W.-H. (2013). Transcriptome analyses show changes in gene expression to accompany pollen germination and tube growth in Arabidopsis. Plant Physiol. 168, 1201–1211. doi: 10.1104/pp.113.230686

Wang, T., Zabotina, O., and Hong, M. (2012). Pectin–cellulose interactions in the Arabidopsis primary cell wall from two-dimensional magic-angle-spinning solid-state nuclear magnetic resonance. Biochemistry 51, 9846–9856. doi: 10.1021/bi3015532

Wang, Y., Zhang, W.-Z., Song, L.-F., Zou, J.-J., Su, Z., and Wu, W.-H. (2008). Salt stress increases the expression of p5cs gene and induces proline accumulation in cactus pear. Plant Physiol. Biochem. 46, 82–92. doi: 10.1016/j.plaphy.2007.10.011

Sotosanto, J. B., Gelli, A., and Blumwald, E. (2004). DNA array analyses of Arabidopsis thaliana lacking a vascular Na+/H+ antipporter: impact of AtNHX1 on gene expression. Plant J. 40, 752–771. doi: 10.1111/j.1365-313X.2004.02253.x
Wellmer, F., Riechmann, J. L., Alves-Ferreira, M., and Meyerowitz, E. M. (2004). Genome-wide analysis of spatial gene expression in Arabidopsis flowers. *Plant Cell* 16, 1314–1326. doi: 10.1105/tpc.021741

Wolf, S., Hématy, K., and Höfte, H. (2012). Growth control and cell wall signaling in plants. *Annu. Rev. Plant Biol.* 63, 381–407. doi: 10.1146/annurev-arplant-042811-105449

Wuest, S. E., Vijverberg, K., Schmidt, A., Weiss, M., Gheyelinck, J., Lohr, M., et al. (2010). *Arabidopsis* female gametophyte gene expression map reveals similarities between plant and animal gametes. *Curr. Biol.* 20, 506–512. doi: 10.1016/j.cub.2010.01.051

Xu, J., Yang, C., Yuan, Z., Zhang, D., Gondwe, M. Y., Ding, Z., et al. (2010). The ABORTED MICROSPORES regulatory network is required for postmeiotic male reproductive development in *Arabidopsis thaliana*. *Plant Cell* 22, 91–107. doi: 10.1105/tpc.109.071803

Xu, P., Cai, X.-T., Wang, Y., Xing, L., Chen, Q., and Xiang, C.-B. (2014). HDG11 upregulates cell-wall-loosening protein genes to promote root elongation in *Arabidopsis*. *J. Exp. Bot.* 65, 4285–4295. doi: 10.1093/jxb/eru202

Yamaguchi, T., and Blumwald, E. (2005). Developing salt-tolerant crop plants: challenges and opportunities. *Trends Plant Sci.* 12, 615–620. doi: 10.1016/j.tplants.2005.10.002

Yan, H., Ma, L., Wang, Z., Lin, Z., Su, J., and Lu, B.-R. (2015). Multiple tissue-specific expression of rice seed-shattering gene SH4 regulated by its promoter pSH4. *Rice* 8, 12. doi: 10.1186/s12284-015-0047-4

Yang, X., Ye, C.-Y., Bisaria, A., Tuskan, G. A., and Kalluri, U. C. (2011). Identification of candidate genes in *Arabidopsis* and *Populus* cell wall biosynthesis using text-mining, co-expression network analysis and comparative genomics. *Plant Sci.* 181, 675–687. doi: 10.1016/j.plantsci.2011.01.020

Ye, Z.-H., Song, Y.-R., Marcus, A., and Varner, J. E. (1991). Comparative localization of three classes of cell wall proteins. *Plant J.* 1, 175–183. doi: 10.1111/j.1365-313X.1991.00175.x

Yokoyama, A., Yamashino, T., Amano, Y.-I., Tajima, Y., Imamura, A., Sakakibara, H., et al. (2007). Type-B ARR transcription factors, ARR10 and ARR12, are implicated in cytokinin-mediated regulation of protoxylem differentiation in roots of *Arabidopsis thaliana*. *Plant Cell Physiol.* 48, 84–96. doi: 10.1093/pcp/pcp040

Youl, J. J., Bacic, A., and Oxley, D. (1998). Arabinogalactan-proteins from *Nicotiana alata* and *Pyrus communis* contain glycosylphosphatidylinositol membrane anchors. *Proc. Natl. Acad. Sci. U.S.A.* 95, 7921–7926. doi: 10.1073/pnas.95.14.7921

Zhu, Y., Dong, A., Meyer, D., Pichon, O., Renou, J.-P., Cao, K., et al. (2006). *Arabidopsis* NRP1 and NRP2 encode histone chaperones and are required for maintaining postembryonic root growth. *Plant Cell* 18, 2879–2892. doi: 10.1105/tpc.106.046490

**Conflict of Interest Statement**: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2017 Ihsan, Ahmad, Shah, Rehman, Aslam, Ahuja, Bones and Ahmad. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) or licensor are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.