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Utilization of hormones as cell signaling component, its mechanism and regulated protein and gene expression

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Abstract
The review study was conducted from different research data to identify the innovative latest information on cell signaling component, mechanism and regulated protein and gene expression in plant and animal growth and development. From the review study results, plant hormones like Auxin, GA_3, cytokinin, ehylene, ABA hormones, animal or human hormones like cytokines, steroid in defined concentration of treatment and the gene expression altered. Auxin, GA and ABA, cytokines, as well as steroid regulated proteins like F-box proteins, and EIN3-Binding F-BOX1 (EBF1) and EBF2 protein, DELLA proteins, DWA1 and DWA2, CUL4-based CRLs, ABI five binding protein, TIR1/AFB proteins and Aux/IAA proteins were described well and found related new genes from different review data.

Keywords: auxin, GA_3, ABA, cytokines, steroid, cell signaling, growth

1. Introduction
Cells usually communicate each other using chemical signals. These chemical signals are proteins or other molecules produced by a responding cell are often secreted from the cell and released into the extracellular space (Khan, 2017) [32]. Cell signaling is the communication process that leads basic activities of cells and coordinates all cell actions in plant, animal and human. The ability of cells to respond to their microenvironment is the basis of development, tissue repair, and immunity, as well as normal tissue homeostasis. Signal transduction is a fundamental cellular process essential for sharing events at the cell surface and interactions with the extracellular environment into changes of gene expression that occur in the nucleus. These events proceed from membrane to nucleus via a series of protein modifications mediated by specific enzymes such as protein kinases (Ralph *et al* 2010) [33]. By understanding cell signaling, diseases may be treated more effectively and artificial tissues may be created (Smith *et al*, 2015) [1]. In the case of cell signaling in plant, cells communicate to coordinate their activities in response to the changing conditions of light, dark, and temperature that guide the plant's cycle of growth, flowering, and fruiting. Plant cells also communicate to coordinate in their roots, stems, and leaves. In this final section, it can be considered how plant cells signal to one another and how they respond to light. Much less is known about the receptors and intracellular signaling mechanisms involved in cell communication in plants, and it can be concentrated mainly on how these differ from those used by animals or human (Hossain and Uddin, 2018a) [10].

1.2 Categories of cell signaling
Basically cell signaling types are mechanical and biochemical process based on the type of the signal. Mechanical signals are the signals having forces exerted on the cell and the forces produced by the cell. Biochemical signals are the signals having biochemical molecules such as proteins, lipids, ions and gases (Miller *et al*. 2013) [2]. It was reported that the types of cell signaling were intracrine signals which were produced by the target cell that stay within the target cell, autocrine signals which were produced by the target cell, were secreted, and affected the target cell itself via receptors, juxtacrine signals target touching cells which signals were transmitted along cell membranes via protein or lipid components integral to the membrane and were capable of affecting either the emitting cell or cells immediately adjacent, paracrine signals target cells which cells in the vicinity of the emitting cell like Neurotransmitters represent and endocrine signals target distant cells: Endocrine cells produce hormones that travel through the blood to reach all parts of the body. (Hossain, 2018, Hossain and Uddin, 2018b) [12, 11].

1.3 Cell signaling Molecules or Components
Hossain *et al*. (2018) [12] stated that hormones are the major signaling molecules of the endocrine system, though they often regulate each other's secretion via local signaling and most are also expressed in tissues for local purposes: Major hormones are auxin, gibberellin, ethylene, cytokinin and abscissic acid.

1.3.1. Indole acetic acid (auxin/IAA)
Calderón Villalobos *et al*. (2012) [6] stated that auxin was directly bound by both TIR1/AFB and an Aux/IAA protein simultaneously and thus created a “coreceptor” complex Additionally, the binding affinity of auxin appeared to be predominantly controlled by the Aux/IAA proteins and not the TIR1/AFB proteins (Calderón Villalobos *et al*., 2012) [6]. A 13-amino acid motif known as the degron located within domain II of Aux/IAA proteins (Ramos *et al*., 2001) contributed to substrate stability and turnover rates that range from approximately 10 to 80 min (Dreher *et al*., 2006). The varied protein-protein interaction affinities between TIR1/AFB proteins and Aux/IAA proteins (Calderón Villalobos *et al*., 2012) [6] combined with

distinct spatiotemporal patterns of accumulation (Parry *et al*., 2009; Vernoux *et al*., 2011) [21, 28] might contribute to the broad role of auxin in diverse growth processes. Almost every aspect of plant growth and development was controlled by auxin signaling (Stewart and Nemhauser, 2010). The role of UPS activity in the auxin response had been extensively studied and was well established (Santner *et al*., 2009; Shan *et al*., 2012) [24]. Figure 1 showed the auxin signaling in plant (Vanneste and Friml, 2012) [30].

1.3.2. Gibberellic Acid (GA3)

Gao *et al*. (2011) [13] reported that SCF-mediated regulation had been shown for GA signaling. The effects of GA included promotion of seed germination, stimulation of organ elongation, and induction of flowering. GA was perceived by a protein called gibberellin insensitive dwarf1 (GID1). GA binding to GID1 resulting in binding to nucleus-localized growth repressors called DELLA proteins (Ueguchi-Tanaka *et al*., 2005; Nakajima *et al*., 2006; Willige *et al*., 2007). This tripartite GID-GA-DELLA complex was subsequently targeted for ubiquitylation by SCFSLY1/SNZ E3 ligases, resulting in degradation of the DELLAs (Gao *et al*., 2011) [13]. This scenario was reminiscent of UPS action during auxin and JA-Ile signaling, because DELLA proteins bind and repressed the activity of transcription factors such as the Phytohormone interacting factors (de Lucas *et al*., 2008; Feng *et al*., 2008) [8, 9].

1.3.3. Cytokinin

Hossain *et al* (2018) [12] stated that two types of cytokinins: adenine-type cytokinins represented by kinetin, zeatin, and 6-benzylaminopurine, and phenylurea-type cytokinins like diphenylurea and thidiazuron (TDZ). Most adenine-type cytokinins were synthesized in roots (Hossain and Uddin, 2018b) [11]. Cambium and other actively dividing tissues also synthesize cytokinins. The effects of cytokinin include promotion of growth of shoot, stimulation of organ elongation, and induction of flowering. Cytokines are signaling molecules of the immune system, with a primary paracrine or juxtacrine role, though they can during significant immune responses have a strong presence in the circulation, with systemic effect (altering iron metabolism or body temperature). Growth factors can be considered as cytokines or a different class (Hossain and Uddin, 2018b) [11].

1.3.4. Ethylene

Schaller (2012) [26] suggested that a number of enzymes involved in ethylene biosynthesis were targeted for proteasomal degradation. This includes (1) type-2 1-aminocyclopropane-1-carboxylic acid synthase proteins (ACS4, ACS5, and ACS9), which were ubiquitylated by ETO1 and ETO-like1/2 BTB ligases (Yoshida *et al*., 2005) [29], and (2) ACS7, a type-3 ACS enzyme that was ubiquitylated by the RING-type E3 ligase XBAT32 (Lyzenga *et al*., 2012) [19]. These degradation mechanisms provided a rapid way to change ethylene concentrations in planta. In the presence of ethylene, ETP expression was repressed, allowing the accumulation of EIN2. Downstream of EIN2 lies EIN3 and EIN3-like1 (EIL1), transcription factors that directly target ethylene-responsive genes. At low ethylene levels, EIN3 and EIL1 were targeted for ubiquitylation and degradation by another pair of F-box proteins, EIN3-BINDING F-BOX1 (EBF1) and EBF2 were also subjected to proteasomal degradation (Guo and Ecker, 2003; Potuschak *et al*., 2003; An *et al*., 2010) [15].

1.3.5. Abscissic Acid (ABA)

ABA biosynthesis were controlled by protein degradation. ABA played an important roles in many physiological processes, including seed germination and stress responses, both biotic and abiotic. The current understanding of ABA signaling, from receptors to responses, included many intermediate steps and was quite complex (Cutler *et al*., 2010; Kim, 2012) [7, 16]. At least one ligase had been shown to directly impact ABA biosynthesis. In thaliana plant U-BOX44 (AtPUB44) regulated the levels of abscissic aldehyde oxidase3, an enzyme that converted abscisic aldehyde to ABA (Raab *et al*., 2009) [23]. Another gene that had been shown to affect ABA levels was XERICO, which encoded a RING-H2 domain-containing protein that could interact with UPS components in yeast, including the F-box tubby lke protein-9 (Ko *et al*., 2006). The levels of ABA insensitive (ABI5), a basic Leu zipper transcription factor, were regulated by at least two different classes of E3 ligases, DWA1 and DWA2, CUL4-based CRLs (Stone *et al*., 2006; Lee *et al*., 2010). The nucleus-localized ABI five binding protein (AFP) family appears to promote ABI5 degradation in nuclear bodies in concert with the RING protein COP1, although it was not exactly clear how this process occurs (Lopez-Molina *et al*., 2003).

1.3.6 Other Hormones

A couple of key components of BR signaling appear to be degraded by the 26S proteasome in response to BR by unknown ligases (Fig. 1F). Specifically, the brassinosteroid insensitive 2 (BIN2) kinase is regulated by proteasome-mediated protein degradation (Peng *et al*., 2008). Additionally, the transcription factor BZR1 is phosphorylated by BIN2 and rapidly degraded by the proteasome to mediate the feedback inhibition of several BR biosynthetic genes (He *et al*., 2002). A recent report also demonstrated that the endoplasmic reticulum-associated protein degradation pathway controls levels of the BR receptor BIN1 via a stress-induced ubiquitin conjugation enzyme, UBC32 (Cui *et al*., 2012). UPS activity is implicated in SL signaling because more axillary branches 2 (MAX2) encodes an F-box protein (Stirnberg *et al*., 2002). A direct role for the UPS in cytokinin action has not been described. However, the recent identification of auxin up-regulated F-box protein 1 (AUF1) implicates $SCF^{AUF1/2}$ in mediating interactions between cytokinin and auxin (Zheng *et al*., 2011). Given the extent of protein degradation for other hormones, the identification of MAX2 and AUF1/2 targets should prove to be quite interesting.

1.3.7 Neurotransmitters

They are signaling molecules of the nervous system, also including neuropeptides and neuromodulators. Neurotransmitters like the catecholamines are also secreted by the endocrine system into the systemic circulation (Hossain, 2018).

1.4. Signaling mechanism

Dinasarapu *et al* (2011) [3] described the cell signaling mechanism that a signal transduction mechanism or pathway shown in Fig. 1. This pathway involved the change of protein to protein interactions inside the cell, induced by an external signal. Many

growth factors bind to receptors at the cell surface and stimulate cells to progress through the cell cycle and division. Several of these receptors are kinases that start to phosphorylate themselves and other proteins when binding to a ligand. This phosphorylation can generate a binding site for a different protein and thus induce protein to protein interaction. In Figure 1, the ligand (called epidermal growth factor (EGF)) binds to the receptor (called EGFR). This activates the receptor to phosphorylate itself. The phosphorylated receptor binds to an adaptor protein (GRB2), which couples the signal to further downstream signaling processes. For example, one of the signal transduction pathways that are activated is called the mitogen-activated protein kinase (MAPK) pathway. The signal transduction component labeled as MAPK in the pathway was originally called ERK, so the pathway is called the MAPK/ERK pathway. The MAPK protein is an enzyme, a protein kinase that can attach phosphate to target proteins such as the transcription factor MYC and, thus, alter gene transcription and, ultimately, cell cycle progression. Many cellular proteins are activated downstream of the growth factor receptors for example, EGFR that initiate this signal transduction pathway.

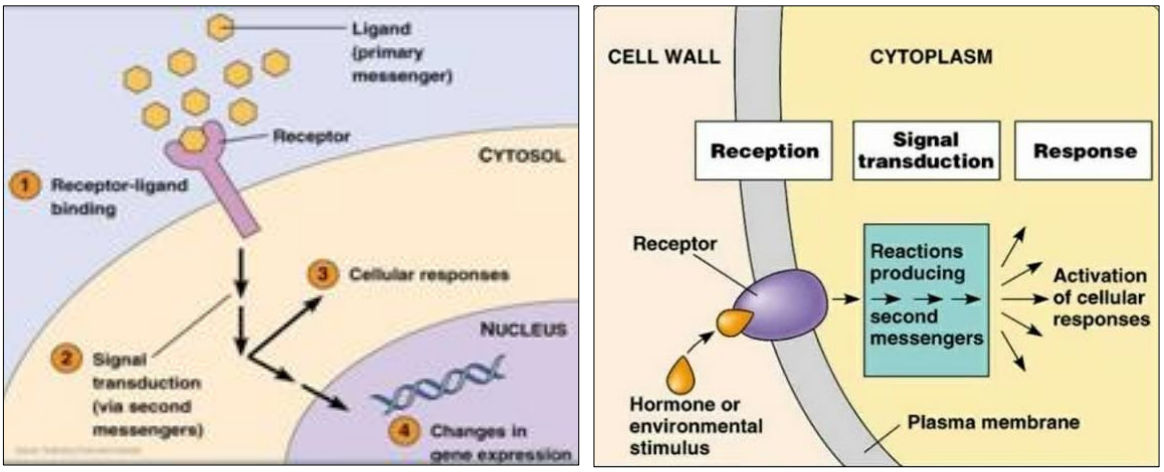

Fig 1: Cell signal transduction pathway or mechanism. https://www.google.co.uk/search?q=a+signal+transduction+mechanism+or+pathway&safe=strict&source.https://www.pinterest.com/pin/774548835894893045/https://www.mun.ca/biology/desmid/brian.

Some signaling transduction pathways respond differently, depending on the amount of signaling received by the cell. For example, the hedgehog protein activates different genes, depending on the amount of hedgehog protein present. Sometimes, receptor activation caused by ligand binding to a receptor is directly coupled to the cell's response to the ligand. As for example, the neurotransmitter GABA can activate a cell surface receptor that is part of an ion channel. GABA binding to a $GABA_A$ receptor on a neuron opens a chloride-selective ion channel that is part of the receptor. $GABA_A$ receptor activation allows negatively charged chloride ions to move into the neuron, which inhibits the ability of the neuron to produce action potentials. The activated receptor must first interact with other proteins inside the cell before the ultimate physiological effect of the ligand on the cell's behavior is produced. The entire set of cell changes induced by receptor activation is called a signal transduction mechanism or pathway (Dinasarapu, 2011) [3].

1.5. Cytokines signaling in mammal cell

Cytokines are a large group of proteins, peptides or glycoproteins that are secreted by specific cells of immune system. Cytokines are signaling molecules of the immune system, with a primary paracrine or juxtacrine role though they can immune during significant responses have a strong presence in the circulation, with systemic effect. Cytokines are a category of signaling molecules that mediate and regulate immunity, inflammation and hematopoiesis. Growth factors can be considered as cytokines or a different class. Cytokines are a broad and loose category of small proteins (~5–20 kDa) that are important in cell signaling. They have an effect on the behavior of cells around them. It can be seen that cytokines are involved in autocrine signaling, paracrine signaling and endocrine signaling as immunomodulating agents. Cytokines may include chemokines, interferons, interleukins, lymphokines, and tumour necrosis factors but generally not hormones or growth factors. Cytokines are produced by a broad range of cells, including immune cells like macrophages, B lymphocytes, T lymphocytes and mast cells, as well as endothelial cells, fibroblasts, and various stromal cells; a given cytokine may be produced by more than one type of cell (John, 2010)**.**

1.6. Steroid signaling in mammal cell

Steroid hormone is a steroid that acts as a hormone. Steroid hormones can be grouped into two classes: corticosteroids which made in the adrenal cortex, hence cortico and sex steroids which made in the gonads or placenta (Beato *et al*. 1996). Steroid hormones influence the transcription of a large number of genes by virtue of their interaction with intracellular receptors, which are modular proteins composed of a ligand binding domain, a DNA binding domain, and several transactivation functions distributed along the molecule. Steroid hormones are transported through the blood by being bound to carrier proteins—serum proteins that bind them and increase the hormones' solubility in water. Some examples are sex hormone-binding globulin (SHBG), corticosteroid-binding globulin, and albumin. Most studies say that hormones can only affect cells when they are not bound by serum proteins. They are secreted by three *steroid* glands like the adrenal cortex, testes, and ovaries and during

pregnancy by the placenta. All *steroid hormones* are derived from cholesterol.

1.7. Mechnism of action of steroid hormone

The mechanism of steroid hormone action is the genomic effects. In this pathway, the free hormones first pass through the cell membrane because they are fat soluble. In the cytoplasm, the steroid may or may not undergo an enzyme-mediated alteration such as reduction, hydroxylation, or aromatization. Then the steroid binds to a specific steroid hormone receptor, also known as a nuclear receptor, which is a large metalloprotein which form one functional DNA-binding unit that can enter the cell nucleus. Once in the nucleus, the steroid-receptor ligand complex binds to specific DNA sequences and induces transcription of its target genes (Gupta, 2002; Linda, 2010; Moore, 1995).

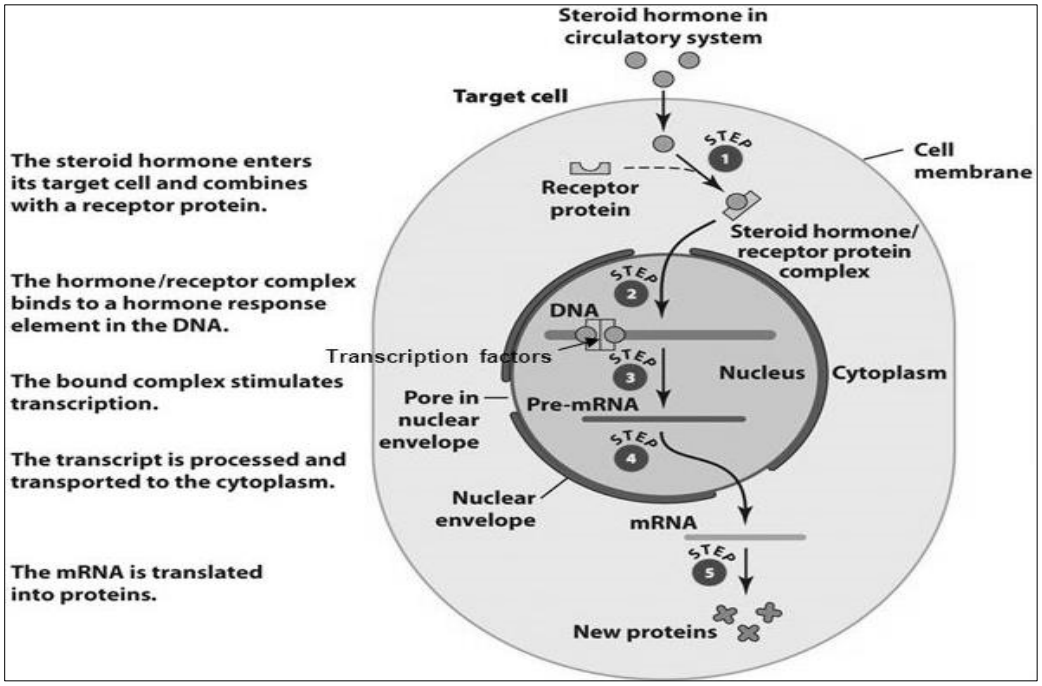

Fig 2: Regulation of gene expression by steroid hormone (https://www.google.com.sa/search?q=gene+expression+steroid+hormone&safe)

1.8. Hormonal regulation of Gene Expression

In mammals hormones can be proteins or steroids. The protein hormones do not enter the cell, but bind to receptors in the cell membrane and mediate gene expression through intermediate molecules. Steroids, though actually enter the cell and interact with steroid receptor proteins to control gene expression. Glucocorticoid hormone is one type of steroid whose method of controlling gene expression has been determined. The steroid interacts with a receptor protein, and this interaction serves two function. First, binding stimulates the release of the protein Hsp90 that is bound to the receptor protein. When Hsp90 is bound to the receptor protein, gene expression is not activated. This would be expected, if the steroid is the signal required for the expression of specific genes in the tissue. A number of steroid receptor proteins have been characterized, and a number of features are in common among them. First, the N-teriminal region of the protein is required to activate transcription in some manner, but the mechanism is not known. This is the least conserved region among the eight proteins. The central portion of the protein is required for DNA binding, and this region is highly conserved (42-94% amino acid). The C-terminal region is required for steroid binding and is moderately conserved (15-52% amino acid). This overall conservation suggests that an ancestral gene may have been the model for each of these genes (NDSU, 1997).

2. References

1. Smith RJ, Koobatian MT, Shahini A, Swartz DD, Andreadis ST. "Capture of endothelial cells under flow using immobilized vascular endothelial growth factor". Biomaterials. 2015; 51:303–12.
2. Miller Callie Johnson, Davidson Lance A. "The interplay between cell signalling and mechanics in developmental processes". Nature Reviews Genetics. 2013; 14(10):733–744. doi:10.1038/nrg3513. ISSN 1471-0056. PMC 4056017. PMID 24045690.
3. Dinasarapu AR, *et al*. "Signaling gateway molecule pages—a data model perspective". Bioinformatics. 2011; 27(12):1736–1738.doi:10.1093/bioinformatics/btr190. PMC 3106186. PMID 21505029.
4. An C, Mou Z. Salicylic acid and its function in plant immunity. J Integr Plant Biol. 2011; 53:412–428.
5. An F, Zhao Q, Ji Y, Li W, Jiang Z, Yu X, *et al*. Ethylene-induced stabilization of ethylene insensitive 1 and EIN3-LIKE1 is mediated by proteasomal degradation of EIN3 binding F-box 1 and 2 that requires EIN2 in Arabidopsis. Plant Cell. 2010; 22:2384–2401.
6. Calderón Villalobos LI, Lee S, De Oliveira C, Ivetac A, Brandt W, Armitage L, *et al*. A combinatorial TIR1/AFB-Aux/IAA co-receptor system for differential sensing of auxin. Nat Chem Biol. 2012; 8:477–485.

7. Cutler SR, Rodriguez PL, Finkelstein RR, Abrams SR. Abscisic acid: emergence of a core signaling network. Annu Rev Plant Biol. 2010; 61:651–679.
8. De Lucas M, Davière JM, Rodríguez-Falcón M, Pontin M, Iglesias-Pedraz JM, Lorrain S. A molecular framework for light and gibberellin control of cell elongation. Nature. 2008; 451:480–484.
9. Feng S, Martinez C, Gusmaroli G, Wang Y, Zhou J, Wang F, *et al*. Coordinated regulation of Arabidopsis thaliana development by light and gibberellins. Nature. 2008; 451:475-479.
10. Hossain ABMS, MS Uddin. Cell Biology: Structure, Function and Cell Signaling. LAP Lambart Academic publishing Co. Paperback, Germany, 2018a, p393.
11. Hossain ABMS, MS Uddin. Hormone Regulated Gene Expression: Transcription, translation and Genomics. LAP Lambart Academic publishing Co. Paperback, Germany, 2018b, p130.
12. Hossain ABMS. Natural cytokinin and abscissic acid (ABA) hormones isolation and its effect as growth promoter and inhibitor on callus cell in vitro and phloem tissue of peach plant in vivo. International Journal of Science and Research Methodology. 2018; 9(1):201-210.
13. Gao XH, Xiao SL, Yao QF, Wang YJ, Fu XD. An updated GA signaling 'relief of repression' regulatory model. Mol Plant. 2011; 4:601-606.
14. Greenham K, Santner A, Castillejo C, Mooney S, Sairanen I, Ljung K. The AFB4 auxin receptor is a negative regulator of auxin signaling in seedlings. Curr Biol. 2011; 21:520–525.
15. Guo H, Ecker JR. Plant responses to ethylene gas are mediated by SCF (EBF1/EBF2)-dependent proteolysis of EIN3 transcription factor. Cell. 2003; 115:667–677.
16. Kim TH. Plant stress surveillance monitored by ABA and disease signaling interactions. Mol Cells. 2012; 33:1–7.
17. Lechner E, Leonhardt N, Eisler H, Parmentier Y, Alioua M, Jacquet H. MATH/BTB CRL3 receptors target the homeodomain-leucine zipper ATHB6 to modulate abscisic acid signaling. Dev Cell. 2011; 21:1116–1128.
18. Lopez-Molina L, Mongrand S, Chua NH. A postgermination developmental arrest checkpoint is mediated by abscisic acid and requires the ABI5 transcription factor in Arabidopsis. Proc Natl Acad Sci USA. 2001; 98:4782–4787.
19. Lyzenga WJ, Booth JK, Stone SL. The Arabidopsis RING-type E3 ligase XBAT32 mediates the proteasomal degradation of the ethylene biosynthetic enzyme, 1-aminocyclopropane-1-carboxylate synthase 7. Plant J. 2012; 71:23–34.
20. Miller MJ, Vierstra RD. Mass spectrometric identification of SUMO substrates provides insights into heat stress-induced SUMOylation in plants. Plant Signal Behav. 2011; 6:130–133.
21. Parry G, Calderon-Villalobos LI, Prigge M, Peret B, Dharmasiri S, Itoh H. Complex regulation of the TIR1/AFB family of auxin receptors. Proc Natl Acad Sci USA. 2009; 106:22540–22545.
22. Pauwels L, Barbero GF, Geerinck J, Tilleman S, Grunewald W, Pérez AC, *et al*. NINJA connects the co-repressor TOPLESS to jasmonate signalling. Nature. 2010; 464:788–791.
23. Raab S, Drechsel G, Zarepour M, Hartung W, Koshiba T, Bittner F. Identification of a novel E3 ubiquitin ligase that is required for suppression of premature senescence in Arabidopsis. Plant J. 2009; 59:39–51.
24. Santner A, Calderon-Villalobos LI, Estelle M. Plant hormones are versatile chemical regulators of plant growth. Nat Chem Biol. 2009; 5:301–307.
25. Saracco SA, Hansson M, Scalf M, Walker JM, Smith LM, Vierstra RD. Tandem affinity purification and mass spectrometric analysis of ubiquitylated proteins in Arabidopsis. Plant J. 2009; 59:344–358.
26. Schaller GE. Ethylene and the regulation of plant development. BMC Biol. 2012; 10:9.
27. Schwanhäusser B, Busse D, Li N, Dittmar G, Schuchhardt J, Wolf J. Global quantification of mammalian gene expression control. Nature. 2011; 473:337–342.
28. Vernoux T, Brunoud G, Farcot E, Morin V, Van den Daele H, Legrand J, *et al*. The auxin signalling network translates dynamic input into robust patterning at the shoot apex. Mol Syst Biol. 2011; 7:508.
29. Yoshida H, Nagata M, Saito K, Wang KL, Ecker JR. Arabidopsis ETO1 specifically interacts with and negatively regulates type 2 1-aminocyclopropane-1-carboxylate synthases. BMC Plant Biol. 2005; 5:14.
30. Zhang X, Garreton V, Chua NH. The AIP2 E3 ligase acts as a novel negative regulator of ABA signaling by promoting ABI3 degradation. Genes Dev. 2005; 19:1532–1543.
31. Steffen Vanneste, Jiří Friml. Plant signaling: Deconstructing auxin sensingNature chemical biology, 2012. DOI:10.1038/nchembio.943
32. Khan Academy, 2017. https://www.khanacademy.org/science/biology/cell-signaling/mechanisms-of-cell-signaling/a/introduction-to-cell-signaling.
33. Ralph A Bradshaw, Edward A. Dennis, in Handbook of Cell Signaling (Second Edition), 2010. https://www.Sciencedirect.com/topics/neuroscience/cell-signaling.