REVIEW

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Salicylic acids

Local, systemic or inter-systemic regulators?

Shamsul Hayat,[1,2,*] Mohd Irfan,[1] Arif Shafi Wani,[1] Mohammed Nasser Alyemeni[2] and Aqil Ahmad[1]

[1]Plant Physiology Section; Department of Botany; Aligarh Muslim University; Aligarh, U.P. India; [2]Department of Botany & Microbiology; Faculty of Science; King Saudi University; Riyadh, Saudi Arabia

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Abbreviations: APX, ascorbate peroxidase; AsA, ascorbic acid; CAT, catalase; GR, glutathione reductase; GSH, glutathione (reduced); HR, hypersensitive response; JA, jasmonic acid; MeSA, methyl salicylic acid; NO, nitric acid; NPR1, non-expresser of PR1; PCD, programmed cell death; PGPRs, plant growth promoting rhizobacteria; POX, peroxidase; PR1, pathogenesis related (gene) 1; ROS, reactive oxygen species; SABP, salicylic acid binding protein; SAMT1, salicylic acid carboxyl methyl-transferase 1; SAR, systemic acquired resistance; SOD, superoxide dismutase; TMV, tobacco mosaic virus

Salicylic acid is well known phytohormone, emerging recently as a new paradigm of an array of manifestations of growth regulators. The area unleashed yet encompassed the applied agriculture sector to find the roles to strengthen the crops against plethora of abiotic and biotic stresses. The skipped part of integrated picture, however, was the evolutionary insight of salicylic acid to either allow or discard the microbial invasion depending upon various internal factors of two interactants under the prevailing external conditions. The metabolic status that allows the host invasion either as pathogenesis or symbiosis with possible intermediary stages in close systems has been tried to underpin here.

Introduction

Hormones are the biochemical language of living systems. These in either of the plant or animal system perform fundamentally similar function; the integration of system at basal economy level. Classically, plant hormones have been defined as low molecular weight organic compounds governing pleotropic physiological responses within plants, but distant from the sites of their synthesis. Their extreme low (mM to μM) concentrations are sufficient to elicit multifaceted responses in different tissues types that shares expression of specific receptors within cytosol and/or on membranes. Where on one hand their binding to receptors elicits amplified downstream signal cascades, the population of receptors expressed inter-/intra-cellularly play crucial role to sense, thereby, subsequently determine the extent/speed of response in tissue types.

Passing decades coarsely witnessed three types of hormonal systems embodied by animals viz. endocrinal, pericrinal and autocrinal based on the distance they travel to site of action. In plants with the introduction of new class of regulators inconsistencies emerged regarding the assignment of their places in the category of plant hormones. The blurred boundaries of these new-comers asked reconsideration of previous definition of phyto-hormones. However, plants studies recently leaped to introduce new regulators which not only act at short distance, their μM concentrations are sufficient to elicit marked physiological and molecular alterations. Interestingly, some other of them shown to travel in air par-systematically mimicking as volatile 'plant-pheromones' (regulating defense e.g., methyl salicylate, jasmonates, strigolactones) or as gaseous molecules (ethylene, NO) switching other essential developmental traits within a part, complete plant or even whole population in-chorus to regulate defense.[1-4] Plants being sessile have to withstand a plethora of biotic invasions coupled with abiotic stressors. The synergy of later with either of plant or microbes disables the interaction of one with another, or may sometimes the equilibrium of trio persist as a long-duration-compromise. Inconsistencies arise with the elucidation of role and mechanism of action of certain short distance regulators viz. steroids; nitric acid and ROS; and intersystemic regulators as salicylic acid, jasmonic acid and strigolactones etc.

These glycosides of salicylic alcohol were first isolated by Johann Buchner in 1828 and called as Salicine has traveled long way since their discovery to establish themselves as distinct class of plant hormone,[5] the salicylic acid. The ubiquitous distribution both in monocots and dicots reflects their importance among plant kingdom.[6] Salicylic acids are peculiar to their type govern plant growth and development under natural and abiotically stressed environmental regimes. These phenolics seems to be transported from the site of application[5] in their transportable form and enhance plant growth and yield, message inter-/intracellularly, systemically, and even par systemically under biotic stress when challenged with invading microbes to prevent the loss of host population. These reportedly interact with different classical and newly recognized plant hormones to regulate diverse metabolic and physiological function[7] in metabolically active tissues or those which are under stress to maintain cellular redox homeostasis from oxidative stress. The elucidation of role of salicylic acid is a challenge in understanding their natural selection

*Correspondence to: Shamsul Hayat; Email: shayat@lycos.com
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and evolution in establishment of two opposite phenomenon, the symbiosis (-a positive interaction) and pathogenesis (-the negative interaction) through all their intermediates (-incompatible interactions, secondary host, attenuation, facultatism etc.). The knowledge how they regulate interplant signaling in different pathogenic and symbiotic relationships is scarce and still elusive.

Evolutionary Importance of Appearance of Salicylic Acid and Their Analogs

Plant physiology encompasses the functional domain of metabolic manifestation of biochemical processes within the plant which in turn get regulated at molecular level. Despite being visibly demarked as compartmentalized cells, tissue types and different systems etc., a remarkable coherence is obvious within such subsystems. The appearance of integrative key molecules initially served here the crucial part of "systemic integration" that backed the complex life to supersede their evolutionary ancestors in the race of competitive selection of survival in aquatic ecosystems and on land later on. Nature, though in part, kept on imparting the selective pressure over generations to sieve the best fit in the long run of evolutionary race, the secondary metabolites, hence, come forth to reserve their place and evolve the secondary metabolic pathways with their active defense molecules.[8] Their expression, in most cases, albeit remain under regulation of inducible promoter. The boundaries of this integrated system to establish the plant to its functional niche does not culminated here, it ensured its survival extending its signaling to message inter-systemically now studied under inter-plant, plant-microbe and plant-predator relationships. Jasmonates and salicylates are special in their role as they not only regulate the plant physiological functions and systemic immunity, these also prime defense signals[9] even in the population of their ecological community. These signals evidenced to talk with insects and pests in biochemical language counteracting in rhizosphere or phylloplane in complex co-evolved fashion. Nevertheless, the time of bargain under unfavorable environment could compromise the cost of invasion; altering the intensity of attack (-virulence) and resistance level to woven the dual life (pathosystem, parasitism, helotism, commensalism, exo-/endo-symbiosis etc.).

Plant, Invader and Abiotic Stressors (Duration/Intensity): A Synergy of Trio Determines the Nature of Relationship

Several examples in nature represent different stages of interaction of organism of two drastically different taxa, from kingdom to species. It appears positive interaction evolved as adjustment descended from early negative interaction diversified polyphyletically. At first site certain examples appears to be at the stage of establishing positive interactions in favor of host/plant, for instance; lichens, mycorrhizae, corallaoid roots of *Cycas, Nostoc* colonies in *Anthoceros* thallus, *Rhizobium*-legume nodules, *Agrobacterium tumifaeciens* mediated tumors, endosymbiont *Chlorella* in ciliates, endosymbiotic bacteria (which later on accommodated themselves as chloroplast and mitochondria) during evolution of eukaryotic cell, viral genome integration in bacterial and other eukaryotes (-transposons sequences) etc. However, negative interactions of plant with microbes are also very common reducing plant growth, or even survival. A condition unfavorable to either of the interacting organisms renders the two to adjust for the time being till the favorable time returns. Although, single/simple-celled microbes seems quickly adjust these altered conditions as compared with integrated cell systems (here plant system). However, these hostile conditions may persist for long time to imprint the memory in the genome of either of the interactants.

The population of plant systems when shows healthy state it represents their favorable growth conditions. On contrary disease is facilitated by the unfavorable conditions of either of the hostile environment, nutritional scarcity alone or along with beneficiary pathogenic encounter to be termed appropriately as pathogenesis. The synergy of two (abiotic and biotic stressors) deteriorates plant physiology more than either of stress. The favorable conditions of invasion viz. nutritional scarcity, temperature, moisture/humidity, inoculum density and virulence of invader with reference to age/physiological condition and susceptibility of host plant appears to be the critical factors responsible to prime the successful ingression and microbial (/pathogen = disease) establishment, often resulting in malphysiology and reduced yield/growth of plant. In the pyramid of disease progression suggests that 'time' factor imparts critical role in ascertaining the fate of relation between invaders with its host. For instance; (a) relatively quick response of host often leads to restricted damage of host tissue rendering the pathogen incompatible for further growth and establishment (-total resistance), (b) a delayed response may favor invader to grow progressively within the host tissue pushing defense responses and rendering it semi- compatible (c). However, a lack of time-tuned appropriate response and signal components (as in case of sensitive host variety) provided aggressive invasion (virulent strain) may completely indispose plant to total failure against invasion (as evident in disease progression) aiding to establishment of patho-system (pathogenesis).

Precise synchrony of phyto-hormonal network may leads to total discard of invader at site with minimal tissue/cell loss reassuring its nutritional supply after a due phase of lagged growth (case a). However, same could not be the case with compatible system (case c) where a remarkable diversion of nutritional supply hijacked through molded gradient of phyto-hormonal gradient facilitate invaders' growth. The hijackers could express extended phenotype at genomic (integration of DNA segment facilitated by protein regulators, siRNA mediated gene silencing) or proteomic (intruder's effector molecules alter the metabolic pathways favoring its establishment) level.[10] The non-metabolizable microbial produce (-pathotoxins) may lead to severe setback of plant growth progressive tissue death. Between these two extremes a semi-compatible system (b) appears to exist to be considered as quasi/semi-pathosystem. Several secondary hosts could be considered under this category lacking the essential components to support the growth of invader negatively. Plants appear to signal their stressed state inviting these intruders under nutritional or abiotically stressed regimes. Krouk and coworkers[11] opinioned nitrogen signals crucially play with the hormonal feedback during nitrogen acquisition and assimilation and also in root development.

However, with the due passage of time host may acclimate to withstand (facultative) invasion to sustain consecutive relationship (obligatory). The 'microbial produce' may be metabolized by host to support its vital functions over generations to develop symbiotic relationship in future (**Fig. 1**).

Functional Validation of Salicylic Acid as a Plant Defense Hormone

Studies revealed the major role of salicylic acid in plants counteracting the biotic stress responses. White[12] first evidenced the involvement of salicylic acid in plant defense. Internal increase in salicylic acid levels during pathogenic plant-microbe interaction often facilitates the building up of the resistance and systemic resistance.[13] Salicylic acid induced resistance against many necrotic or systemic viral, bacterial and fungal pathogens in a variety of plants.[14] Durrant and Dong[9] clearly reviewed the demonstration of salicylic acid accumulation and subsequent role in signaling using mutant and transgenic plants. Bacterial salicylic acid degrading enzyme salicylate dehydroxylase (*NahG*) when overexpressed in transgenic *Arabidopsis* and tobacco plants developed inefficient defense response and showed more susceptibility to pathogen infection damage.[15]

The role of salicylic acid in plants was noticed in the induction of SAR against pathogens.[16] Although, their analogs have also been proved outstanding, defending plant against abiotic stresses[17] to secure their development[18] under suboptimal conditions. Huang et al.[19] analyzed quantitative in situ assay of salicylic acid in tobacco leaves using a genetically modified biosensor strain of *Acinetobacter species* ADP1. The naturally occurring salicylic acid responsive *sal*-operon in the strain was constructed with ADPWH_lux which induced bioluminescence sensing salicylic acid even in concentration as low as 5 nM. The spatial and temporal pattern of increased free salicylic acid and MeSA accumulation in leaves was reported before and after the appearance of the HR elicited by TMV in tobacco. Salicylic acid accumulation was also detected during compatible and incompatible interactions between tobacco and *Pseudomonas syringeae*. The increased accumulation of salicylic acid in pre-necrotic tissue corresponds to pre-HR physiological effects such as local increases in temperature, transpiration rate and alterations in chlorophyll fluorescence.[20,21]

Salicylic Acid Regulates the Fundamental Processes of Plant, the Photosynthesis and Energy Economy

It is recognized that salicylic acid potentially generates a wide array of metabolic responses in plants and also affects photosynthetic parameters and plant water relations. These responses could be either pathogen induced[3,4] mal-physiological responses; restricting plant growth and survival based upon pathogen type, could be root mal-nutritional responses[11] or due to plant incompetency to catch up well compatible level of plant hormone network to push abiotic stress(es) as indicative with several studies showing favorable responses of stage, and dose specific responses of different plant hormones; or could be combinations of either of these cases.

A range of favorable physiological responses have been generated by external application to incompatible (sensitive) plants or while these were promoted in compatible (resistant) cultivars. These responses include shift in active biosynthesis of pigments and their subsequent accumulation,[7,22-24] photosynthesis related parameters[25-27] and the activity of associated enzymes[22] and energy economy at the cost of ROS production (discussed later in detail).

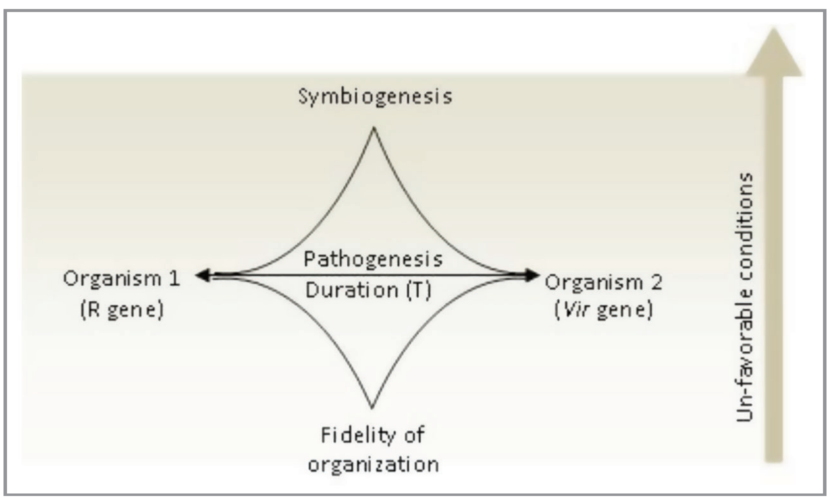

Figure 1. Multiple factors determine the fate of relationship between two interactants (macrobiont and microbiont) i.e., environmental conditions, genotype of two and the time duration.

Inter-Systemic Regulation is Attributed to Methyl Salicylates

The interaction of microbes with plants can induce both local and systemic alterations in the plant.[28] The elevated transcripts level of enzymes of phenylalanine ammonia lyase (PAL) and chalcone synthase (CHS) was clearly implicated specifically in the cells enwrapping arbuscules[29] suggesting local activation of key enzymes of secondary metabolic pathway in vicinity of fungus thalli. However, effect of salicylic acid as SAR led to realization that perhaps it travels through vasculature.[30] However, Vernooji and coworkers[31] strongly favored that salicylic acid is not the signal to induce SAR, though it is require in signaling. Park and others[32] later elegantly demonstrated MeSA as a crucial mobile signal in activation of SAR against TMV. The role of plausible proteins with esterase activity (SABP2) in distal manifestation of SAR and accumulation of MeSA (SAMT1) utilizing inhibitor and mutant study has also been elucidated.[32,33] However, not all plants deploy this strategy of MeSA and JA mediated manifestation of SAR.[34] Those who employ them as a mediator of SAR transport signals through both xylem and phloem.[35] It was seen that in leaves of pathogen infested *Arabidopsis* most (97%) of the MeSA produced has been emitted from plant. However, volatilization of signals could be pathogen induced ploy to mild the SAR induced defense or it could be the plant signaling molded to induce inter-systemic regulation of defense priming SAR in *en masse*.[34] Gutierrez-Luna et al.[36] recently investigated that even PGPR emit volatile organics to modulate root architecture and plant growth. In addition *Arabidopsis* incorporates the JA signaling in response to avirulent pathogen through vasculature conduction.[37] Either of host and microbe seems to overwhelm to counteract each other. The examples of pathogen mediated manipulation of plant defense responses have been suggested time to time.[38]

Inter-/Intra-Cellular Signaling: Reactive Oxygen Species and Salicylic Acids

During cellular metabolic processes, toxic level of reactive oxygen species (ROS) such as superoxide anion (O_2^-), hydroxyl ions (OH·), and hydrogen peroxides (H_2O_2) are generated in aerobic conditions and can cause damage to these cells, a phenomenon known as oxidative stress. When plants are exposed to various environmental stresses they produce range of ROS in large quantities sufficient to disrupt cellular and metabolic functions of the plant. To prevent oxidative injury by the toxic, reactive oxygen species, the activity of antioxidant enzymes such as SOD, APX, GR, POX, CAT and low molecular weight compounds like AsA and GSH is increased normally. For the survival of the plants appropriate functioning of the antioxidant system is important i.e., to maintain a balance between ROS and production and scavenging system.[39] Stress tolerance is therefore related with improved antioxidant system in plants. Previous studies imprints salicylic acid enhances plant antioxidant protective system following logistic growth curve thereby inducing stress tolerance. However, several studies show that higher endogenous concentration of salicylic acid interplays with ROS pushing the cell toward death. Higher concentration of salicylic acid appears to deactivate the antioxidant activity in synergy with ROS. The analysis of peroxysomal antioxidant enzymes viz. SOD, CAT, GPX (Glutathione peroxidase) and AsA-GSH cycle activities in tomato infected with *B. cineria*[40] clearly indicated that initial infection induced increase in SOD, CAT and GPX indicating antioxidant defense activation. It was followed by a progressive inhibition concomitant with disease symptom development.

Accumulating evidence during the last few years raised the idea that salicylic acid interplays with ROS to signal genetic controlled defense reaction such as PCD and expression of stress defense genes. The idea of interplay between salicylic acid and ROS defending stress is now considered crucial for local and systemic defense response.[9,41] Initial rise in endogenous level of salicylic acid supported the idea of upregulating (overexpression and activation) the antioxidative defense system to alter the activity of transcription factors and cellular signaling. However, the supra-optimal level is reported to harm the plant metabolism[26] suggesting oxidation of thiol buffers and activity of low molecular weight transcription factors, thereby suppressing the activity of antioxidant system supporting oxidative burst of ROS. ROS and salicylic acid which accumulate at the high level during HR[42] appears to aid signal amplification for cell death propagation[41] (**Fig. 4**). Apoplastic ROS production[43] in addition to mitochondrial production[39] facilitates PCD. Besides, activating ROS production by several mechanisms[44] salicylic acid also inhibits the activity of antioxidative enzymes such as APX and CAT leading to an over-accumulation of ROS.[45] It has been shown that the accumulation of H_2O_2 is essential for the induction of plant disease resistance, but alone H_2O_2 could not be sufficient to induce program cell death. Exogenous application of salicylic acid causes an increase in H_2O_2 accumulation in plant tissues and their higher H_2O_2 concentration has been proposed to act as a signal inducing HR and SAR against pathogens.[46]

Burst of ROS: Local Defense and Systemic Acquired Resistance

As with the increase or continuous irritation of biotic/metal stress, accumulation of reactive oxygen and nitrogen species increases, the shift in cellular pH and redox state of cytoplasm toward more oxidizing and energetic state elicits change in phosphorylated pool of low molecular weight proteins. Change in oxidative state of cellular components are also facilitate by secondarily produced organic free radicals aids the altered property of membrane and further supporting the decline in pH. Recent technologies emerged to assess the phosphorylated state of the cell cytoplasm under altered conditions what is called as phospho-proteomics. A change in phosphorylated state and Cys residue disulfide bond[39] (oxidation) alters the conformation, thereby, the activity of these low molecular weight proteins. Several of these molecules circumvent the low molecular weight thiol buffers constituting the antioxidant system and transcription factors. The local resistance is facilitated by the initial rise of H_2O_2, augment the defense gene expression.

The intensity of stress (oxidation) for a given duration of time on particular surface area is congregantly counteracted by the efficient management of available basal life sustaining component of cell (house-keeping metabolic processes plus counteracting buffer molecules/enzymes). The management is regulated by the active participation of released/ translocated phyto-hormones. Once oxidative stress crosses the threshold (-a balance between oxidation and induced preventive reduction to prevent minimal required set up for basal metabolic processes), cell switches over toward PCD with simultaneous elicitation of defense mechanisms in neighborhood. Different combinations of hormones and signals (ROS, salicylic acid, JA, NO and H_2O_2) have been proposed to be involved in the initiation, propagation and containment phase of PCD or HR.[41,47] Salicylic acids also mediate the lipid peroxidation, which play a key role in initiating defense response.[48] ROS induced peroxidation of membrane lipids and proteins perturb the homeostasis and induce the de-compartmentation of organelles. Induced ROS level not only have a toxic effect during cell death oxidizing cellular components but additionally constitute proximal (H_2O_2) and distal (methylated forms of salicylic acid and JA) signals to balance information between metabolism and environment.

Plant Interactions with Microbes

Within a community different populations belonging to different taxa interact. These interactions are defined as positive or negative interactions, obligate or facultative relations. The two interactants depending upon the size, mode of feeding and extent of damage reflect gradual trend of conversion of negative interaction to positive relationship through adjustment/attenuation with the passage of time. A highly coordinated molecular dialog between cells of plants and microbe determines the final outcome of the relationship, ranging from pathogenesis to symbiosis,[49] for instance; competition, antagonism, necrotrophism, bionecrotrophism, biotrophism, parasitism, co-operation and endo- or exo-symbiosis etc.

This adjustment involves enforced alteration of metabolism in either of candidate, discovering new signaling of adjustment to live together. The mild oxidative response, genomic and proteomic combat followed by comparative dominance of either of partner. The learning imprints the epigenome and/or genome for further chance interactions culminating into the permanent integration. Microbes are most abundant life forms, the simple structural base of all three major domains of multicellular life. In early intrusion host (-here plant) tries to ensure its organizational fidelity. The genomic, epigenomic or environmental bargaining results into different intermediate interactions to inculcating into more complex life (**Fig. 2**).

Symbiosis verses Pathogenesis; Do Salicylates Have Any Role?

Nature imparts the selective pressure on organisms which is determined by the alteration in prevailing conditions in their niche. This pressure may be a flash of stress or persists for long duration. Struggle for existence may attenuate the defense of two organisms to co-operate for survival discovering new signaling pathways under enhanced rate of spontaneous mutations. The rhizoshpere/rhizoplane or opportunistic microbial intruders seek undue advantage of suboptimal or stressed conditions of their plant hosts through specific airborne or rhizogenic signals.

The epigenomic attenuating regulation gets fixed with the passing generations to strengthen the co-operation shuffling proteome and/or genome vertically or horizontally to stabilize the invasion stress for the genesis of new life organization. In Agrobacterium mediated induction of crown gall; integration of

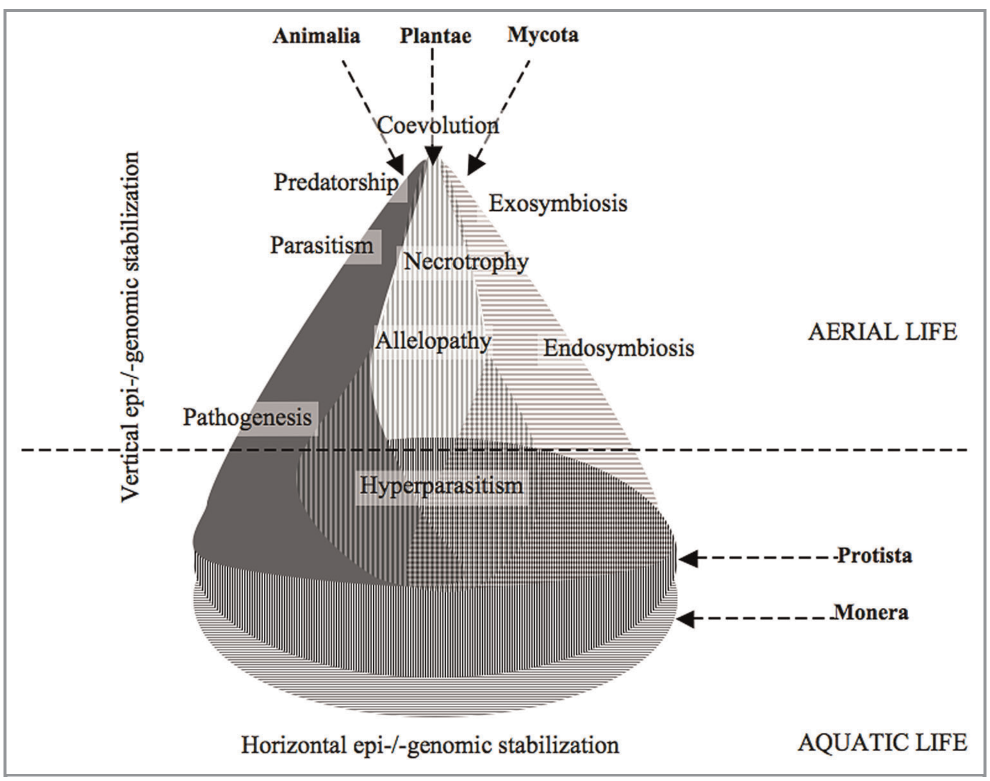

Figure 2. Major biological kingdoms interacts though simple organization/microbes (at base) more commonly with three multi-organized kingdoms to co-evolve chronologically diverse interactions in the nature. The horizontal genetic interchange is seems to be stabilized by the vertical gene transfer and epigenetic expressions under diverse environmental regimes on earth.

T-DNA is facilitated by the early delivery of regulatory proteins in the host cell through pilus.[50] This sym-biogenesis may domesticate primitive lives endogenously in a mutually beneficial capture (prokaryotes within ciliates, zooxanthalleae in coral reefs, coralloid roots of *Cycas* etc.), or enwrapped around the macrosymbiont (mycorrhizae and lichens etc.). It is now accepted that evolution of eukaryotic cell has taken place as a chimera of certain prokaryotic even viral parts. Several examples distributed within and among kingdoms where higher and lower eukaryotes and prokaryotes interact negatively or positively with different level of attenuation of either or both interactants.

A keen study of pathogenetic systems suggests different level of class of interactions depending upon virulent attack and/or resistance capacity. The later appears to me more proteomic/epigenetic rather genomic scarcity to defend them. It has been seen that prior mild exposure builds up internal regulatory molecule in host to heighten its response against secondary encounter and resistance thereby. From invader perspective loose genomic scaffold to express and rapid rate of perpetuation favors the chance of acclimated/adapted strain to survive and populate exponentially. In its niche plant appear to invite the edaphic flora, both positive interactants and negative interactants. The *Nod* and *Myc* factors have been secreted by plants to invite corresponding reactions, whereas, in several angiosperms strigolactones have been secreted to invite parasitic weeds to interact negatively with host.[51]

The interaction of plants with symbiotic microorganisms is largely determined by the endogenous salicylic acid levels. Inoculation of transgenic *Lotus japonicas* and *Medicago truncatula* overexpressing *NahG* with *Mesorhizobium loti* showed increased infection and root nodulation.[52] Studies showed direct effect of salicylic acid on microbes *viz. Sinorhizobium mililoti* (Martinez-Abarca et al., 1998), *Pseudomonas aeruginosa*,[53] *Staphylococcus aureus*[54] and in *Agrobacterium tumefaeciens*.[50] The plant defense responses mounted against *Agrobacterium* are more or less similar to those stimulated by other pathogenic bacteria.[55,56] During the later session of encounter the host defense responses were shown to be hacked by virulent strain.[55] Salicylic acid dually hinders the invasion of pathogenic bacteria, first, triggering the heightened defense responses of plant and second, inhibiting bacterial growth.

Plants discovered salicylic acid perhaps after their encounter to aerial stressed life where they employed salicylates to burst the ROS. The strategy of working of salicylic acid in both the systems (host and invader) is surprisingly similar. However, the loss of adapted cell for invader is more fatal over host with excessive leakage of electrons to generate negative oxygen (via partial reduction of aerobic oxygen). Nevertheless, environmental attenuation of host and promotion (virulence) of invader enabled them to mild the host hypersensitive response to circumvent the defense. Again the persistent co-living may co-operate later to shuffle the proteomic and up to some extent genomic profile rendered the two to live in captured state forever. The molecular details, biochemical adjustment and signal recognition mechanisms we have unraveled until now is only the beginning of uncovered story. The interaction of *Agrobacterium* to induce crown gall or excess rooting, or root nodulation of legumes with *Rhizobium* appear to be the upcoming stories of new symbiotic relation which may fix themselves as new organelles (-nitrosome in case of root nodules) to ensure the constant supply of nitrogen, through hard-to-crack nut of nitrogen fixation.

On the basis of introduction/interaction of plant with microorganism there appear three possible systems. 1) Pathogenic/compatible system (e.g., Biotrophs; *Agrobacterium* crown gall of stem/ hairy root and Bionecrotrophs; *Phytophthora infestans*), 2) Nonpathogenic/incompatible system (e.g., Alternative hosts, *Puccinia graminis* on barberry and other semi resistant hosts 3) Symbiotic systems (e.g., *Rhizobium* legume symbiosis, Mycorrhization with roots of higher plants and PGPRs.

Effect of Salicylic Acid on Plant Defense Responses Against Pathogen

Salicylic acid is regarded as an endogenous marker of plant disease resistance[57] and supposed to be important determinant of pathogenicity. Salicylic acid with its analogs mediates the defense response against a broad spectrum of pathogenic diseases either through exogenous application[58] or endogenously.[59]

The studies on mechanism of salicylic acid action primarily have been focused on plant defense responses.[9] The defense response mediated by the expression of PR1 gene induction.[60] The evidence in this support came through the study of *NahG* mutants overexpressing salicylate hydroxylase which break downs the salicylic acid to catechol. The increased susceptibility of mutants to several pathogens was suggested and earlier evidenced due to hindrance in the expression of PR1.[15] The expression of salicylic acid induced PR genes and SAR primarily promoted by signaling pathway with the involvement of key transcriptional activator NPR1 indicated in *npr1–1* mutant.[60] Inhibition/mutation based hampered salicylic acid biosynthesis resulted in the increased intensity of infection. However, exogenous supplementation of salicylic acid restored their resistance[16] further confirmed the role of salicylic acid in plant defense.

Studies demonstrate that salicylic acid signaling represses expression of auxin related genes by stabilizing auxin response repressors. Salicylic acid signaling counter the ability of plant pathogens to manipulate host auxin metabolism for disease in a tugwar of resistance verses virulence. Salicylic acid, upon infection triggers localized or systemic acquired resistance in which host gains long lasting immunity against pathogen. Early incompatible pathogenic invasion response involves the induction of local host cell death[61] followed by induced resistance protecting plants from subsequent attacks.[62] The auxin physiology in Arabidopsis leaves was shown to be modulated in an infection by *P. syringae*. However, in a compatible pathosystem initial rise of antioxidant system declines subsequently[40] to overwhelm oxidative local death. Amount of free auxin was shown to suppress the host defense against pathogens[63,64] and is associated to disease development.[65] In plant–microbe interactions cytokinins have also emerged as a major candidate during nodule organogenesis and pathogenesis. Cytokinins prompt the salicylic acid accumulation which in turn orchestrates the plant immune response. Choi et al.[3] recently reviewed how pathogen derived cytokinins interferes the plant derived immunity responses checking the auxin growth responses and salicylic acid signaled plant immunity. Although there is no clearcut answer available whether NO induced stomatal opening and bypassed (preventive) cell death during infection is directly modulated by pathogenic factors.

Salicylic Acid Affects Symbiotic Relationships

The still debatable question is how plant recognizes the invader, whether it is a pathogen or a beneficial symbiont? Symbiosis appears to be regulated by clear recognition and precise systematic regulation of host genes in response to initial confirmation of host at least at the proteomic level. The early stages of Rhizobium-legume symbiosis development is reported to be affected by exogenous salicylic acid application.[66] Rhizobia colonizing the roots release the nod factors in response to flavanoids exuded by legumes in rhizosphere, change endogenous salicylic acid content of the host during early nodulation stage. Exogenous salicylic acid inhibit the growth of Rhizobia and the production of nod factors by them and also delay the nodule formation, thereby decreasing the number of nodules per plan.[67] Inoculation of *Medicago sativa* with incompatible strains of Rhizobia resulted in marked increase of endogenous salicylic acid in roots. Contrarily, the compatible strains suppressed salicylic acid accumulation in host roots. It was concluded that later produces certain signals (specific Nod factors) in response, to suppress salicylic acid accumulation.[68] The higher concentration of salicylic acid application (5 and 1 mM) inhibited nodulation and markedly decreased nodule number and their dry mass in assistance with lowered nitrogen fixation and photosynthesis.[69] Also, the lower concentration of exogenous salicylic acid strongly inhibited indeterminate nodulation in *Vicia sativa* and pea thereby decreased nodulation, nitrogen fixation and ultimately growth of plants. Interestingly, the same concentration of salicylic acid when sprayed on *Phaseolus vulgaris, Lotus japonicas* and soybean; formed determinate nodules.

It is very likely that the structure of Nod factor is the key regulator of their bioactivity to be recognized by the receptors of the host. The Nod factors Different *Rhizobium* species share a common basic structure of lipochitosaccharide; a four to five unit backbone of β-1,4-linked N-acyl-D-glucosamine, containing a fatty acid at the non-reducing terminal sugar.[70] Biochemical studies have shown few putative Nod-factor binding proteins, but these are yet not clearly confirmed as Nod-factor receptors.[71]

Another important symbiont of plant roots are arbuscular mycorrhizal (AM) fungi, the member of order Glomales colonizing roots of higher plants symbiotically, improving plant nutrition and water use efficiency, protecting against biotic and metal stress particularly.[72] During early root colonization of AMF defense responses are activated and suppressed subsequently.[59,67] Comparative transcriptome analyses of rice provided an overlap in the response to mycorrhizal fungi and fungal pathogens[73] including some responses associated with defense while some other pointed to common compatibility responses to microbes with diverse lifestyles. Liu and coworkers[29] marked the induction of cysteine rich proteins sharing identity with defensing domain. Studies performed by Yang and colleagues[74] showed induction of nodulin (TC111056), a respiratory burst oxidase (TC100875) and Ntdin (TC107460), a chloroplast protein involved in the synthesis of molybdenum co-factor. Exogenous application of salicylic acid to roots of rice inoculated with AMF reduced inoculation initially during interaction, but on appressoria formation showed no effect. This excludes a direct inhibitory effect of the compound on AMF.[45]

Interestingly, mutants of Nod$^-$ (absence of nodule formation) were also Myc$^-$ (absence of mycorrhization).[75,76] The *sym30* gene mutated in these (P2) plants[75,77] was implicated to share a common pathway suppressing salicylic acid dependent defense in plant against these symbionts.[78] Nod factor suggested to inhibit the salicylic acid mediated defense in alfalfa roots.[68] Gianinazzi-Pearson and coworkers[79] reported at least five separate loci involved in both nodulation and AM formation.

The increasing accumulation of salicylic acid with time in symbiosis-resistant (P2) pea mutants (Nod$^-$, Myc$^-$) for *Rhizobium leguminoserum* and *Glomus mosseae* suggested that salicylic acid accumulation in roots of plants depends upon the inability of bacterium to elicit Nod factors. Furthermore, the two unrelated endosymbionts with drastically different host specificities and symbiotic structures may show convergence of molecular and genetic mechanisms[80,81] (**Fig. 3**).

Molecular and genetic studies show that the infection processes are strikingly similar. Several genes have been identified which are

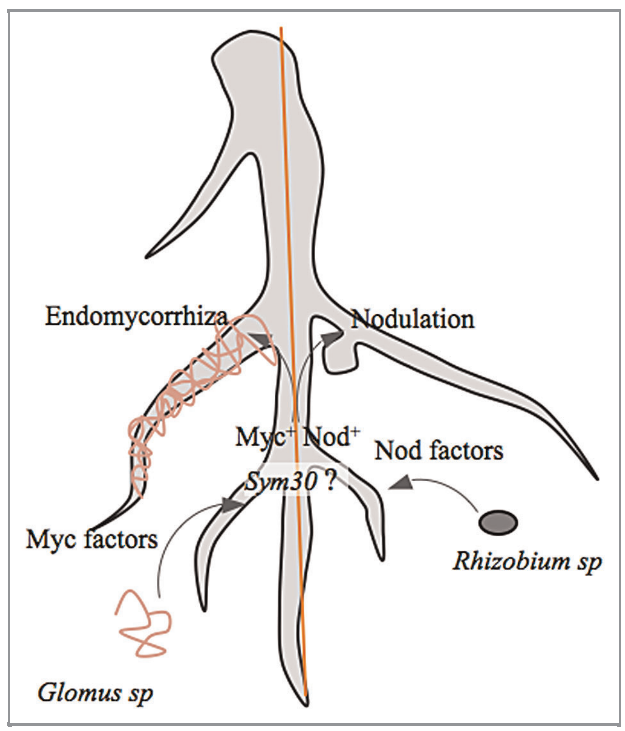

Figure 3. Two most important microbial interactants of plants i.e., root noduling rhizobium and VAM fungi shares the signaling pathways converging at key factors.

induced during both symbiotic interactions, e.g., the early nodulin genes ENOD2, ENOD40,[82] ENOD5, ENOD12,[83] the leg-hemoglobin gene VFLb29[84] and the aquaporin encoding gene NOD26.[85] However, the most convincing evidence that the infection processes used by either of micro-symbionts involve common steps came from studies with legume mutants which have lost the ability to form nodules. A large proportion of the nodulation-resistant mutants were also completely resistant to AM fungi, while their interaction with soil pathogens was not affected.[86,87]

In pea, four genes have been identified that are essential for early steps of both the rhizobial and mycorrhizal interactions. Mutants of three of these genes, *sym8*, *sym9* and *sym19*, have been studied in more detail at a cytological level. These mutants are unable to form an infection thread[88] and although AM fungi still can form appressoria on these Nod$^-$/Myc$^-$ mutants, they fail to develop intercellular hyphae.[86] This shows that rhizobial and mycorrhizal infection involves common mechanisms. The gene ENOD12 is induced in cells involved in, or getting prepared for infection by rhizobia[89,90] and is activated when the fungus infects the roots.[83]

Induction of Biosynthetic Genes and Salicylic Acid Mediated Gene Expression: A Regulatory Affair

The salicylic acid regulates specific kinases and phosphatases to de/activate enzymes (and flux) of specific pathway and their key branching points, the activity of antioxidative enzymes and molecules, the upregulation enzymes of specific pathways as phenylpropanoid pathway (PAL,[91] ICS,[92] polyamine biosynthesis; P5C) and for other osmolytes and ultimately at the expression level the sensors/receptors and specific transcription factors etc. Possibly salicylic acid inhibits pathogen growth repressing the auxin signaling pathways in plants.[65] Evidence shows the manipulated host auxin-biosynthesis by pathogen interfere normal developmental process.[92,93] Plant probably themselves represses auxin signaling to come up with defense strategy during infection, though many pathogens can themselves produce auxins.[94] Wang and coworkers[95] extensively studied the regulatory nodes of SAR at transcriptional level in *Arabidopsis thaliana*. The involvement of NPR1-dependent salicylic acid signaling with WRKY[60] and MYB[96] transcription factors, SABP-2,[97] MRP-type ABC transporters[8] and NPR1-TGA protein complex in activation of salicylic acid responsive elements of PR genes have been recently recognized components of salicylic acid based gene expression regulation and signal transduction cascade.

Future Perspectives

Pests involve plethora of crop feeding pathogens, insects, worms, herbivores and the entire similar category that curtails human consumptionable plants or plant parts. Integrative pest management (IPM) emphasizes to use the term ‘management’ over ‘control’ for pests. We can only manage pests below threshold level to reduce the economic loss as complete elimination of pests is impossible. Life systems are quite intelligent[98] to incorporate acclimation (the temporary adjustment within a generation) and adaptation (permanent modification over generations) to survive and evolve further. Under hostile conditions struggling living systems may intensify the struggle to either totally discard another or live together temporarily or permanently. Nevertheless, crops are grown keeping in mind interests of human beings to reduce negative effects of abiotic and biotic stressors maximally. However, human grown crops are homogenous populations of nutritionally important plants, which invite pests inevitably as an easy, safe and sustained substrate to feed over. Salicylic acid has been evolved as a secondary metabolite to ascertain the integrity of system to resist the external trespass. The recruitment of auxins is more common and economic[99] in plants allowing the systemic integration. The evolution of these interactants appears to follow the history of pre-karyotic invasion of proterobacteria as during the evolution of chloroplasts and mitochondria. This new frontier of research may open the new door in assistance with gene-tailoring and their *in-vitro* stabilization into plants to favor the plant growth yield and quality of produce.

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