Do photosynthetic cells communicate with each other during cell death? From Cyanobacteria to vascular plants

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Highlight

This review explores how cell-cell communication, through “survival” and “death” signals, contributes to the control of the spatiotemporal propagation of cell death in photosynthetic organisms.

Abstract:

As in metazoans, life in oxygenic photosynthetic organisms relies on the accurate regulation of cell death. During development and in response to the environment, photosynthetic cells activate and execute cell death pathways that culminate in the death of a specific group of cells, a process known as regulated cell death (RCD). RCD control is instrumental, as its mis regulation can lead to growth penalties and even the death of the entire organism. Intracellular molecules released during cell demise may act as "survival" or "death" signals and control the propagation of cell death to surrounding cells, even in unicellular organisms. This review explores different signals involved in cell-cell communication and systemic signaling in photosynthetic organisms, in particular Ca^{2+}, ROS, lipid derivates, NO and eATP. We discuss their possible mode-of-action as either "survival" and "death" molecules and their potential role in determining cell fate in neighboring cells. By comparing the knowledge available across the taxonomic spectrum of this coherent phylogenetic group, from cyanobacteria to vascular plants, we aim at contributing to the identification of conserved mechanisms that control cell death propagation in oxygenic photosynthetic organisms.

Keywords: Cell-cell communication, regulated cell death, spatiotemporal propagation, symplast, apoplast, phytoplankton

Introduction

In metazoans, development and homeostasis are regulated by opposing survival and death pathways (Flusberg and Sorger, 2015). Regulated cell death (RCD), a highly coordinated process that relies on a dedicated molecular machinery, plays a major role in nearly every aspect of physiology and in preserving homeostasis under stress conditions (Galluzzi *et al.*, 2015). Signaling related to stress responses often plays a dual role in activating survival pathways that attempt to repair damage and recover homeostasis, as well as in the activation of RCD (Galluzzi *et al.*, 2016). Thus, signaling pathways that regulate cell life and death are tightly linked, and are mediated by several molecules among which some exert both functions (Muñoz-Pinedo, 2012; Flusberg and Sorger, 2015).

Several RCD subroutines have been described and are well-characterized in metazoans (Galluzzi *et al.*, 2018). It is now evident that these subroutines have distinct effects on the surrounding cells and, therefore, affect cell population dynamics. In this sense, RCD can be an autonomous event with no impact on neighboring cells, but it can also affect the viability of surrounding cells either by providing a survival advantage, or inducing cell death (Galluzzi *et al.*, 2018; Riegman *et al.*, 2020). Indeed, some modes of RCD spread between cells and synchronize death across cell populations. (Riegman *et al.*, 2019). For instance, recent studies in mammalian cell lines show that ferroptosis, an iron-dependent RCD characterized by the accumulation of lipid hydroperoxides to lethal levels, propagates cell-cell in a wave-like manner, allowing the elimination of large cell populations (Riegman *et al.*, 2020).

Oxygenic photosynthetic organisms, who, share ancestry through the chloroplast, undergo RCD (Box 1) (Raven and Allen, 2003; Reape *et al.*, 2008; Bidle, 2016; Daneva *et al.*, 2016; Aguilera *et al.*, 2021). RCD is triggered under biotic and abiotic stress in phytoplankton, a diverse group of cyanobacteria (prokaryotes) and eukaryotic microalgae that are central to global primary productivity in aquatic systems (Berges and Choi, 2014; Bidle, 2016; Aguilera *et al.*, 2021; Franklin, 2021). Although less explored, RCD has been described in multicellular algae as well, including colonial chlorophytes and

brown macroalgae (Wang *et al.*, 2004, 2013*b*; Desnitskiy, 2021). Similarly, plants activate RCD during the response to biotic and abiotic stress and rely on RCD to maintain whole-organism homeostasis (Distéfano *et al.*, 2017, 2021; Locato and De Gara, 2018). Since RCD is a common feature of development and adaptation to the environment in photosynthetic organisms, mechanisms must be in place to regulate its execution both temporally and spatially. Furthermore, in photosynthetic organisms, death of one cell might affect the viability of surrounding cells, as described in metazoans (Riegman *et al.*, 2019, 2020). Furthermore, the question emerges of how do photosynthetic organisms coordinate and regulate the death of large groups of cells? Even though there is limited knowledge about mechanisms of death synchronization and propagation in cell populations of photosynthetic organisms, evidence suggests that communication between dying cells may be a more commonly utilized strategy than is currently appreciated.

Here, we review the available data on signaling molecules involved in stress surveillance, systemic signaling, and RCD across the photosynthetic lineage (Fig. 1), with a focus on their survival and death function. We define, as survival those molecules that are secreted by dying cells and prevent RCD in surrounding cells, whereas death molecules will have the opposite effect and induce RCD in neighboring cells. We also discuss potential mechanisms of RCD synchronization and propagation in photosynthetic organisms, including prokaryotic and eukaryotic phytoplankton, macroalgae and vascular plants.

Cell-cell communication and RCD in photosynthetic organisms

During the evolution of both unicellular and multicellular organisms, the actively controlled demise of cells (also termed PCD and RCD, see Box 1) has been recruited to fulfill a variety of functions such as development, differentiation, response to environmental stress, and maintaining whole-organism homeostasis (Ameisen, 2002). A large body of evidence demonstrates that heterotrophic bacteria

evolved different forms of RCD that play important roles in developmental programs (see Lewis, 2000; Ameisen, 2002 and references therein). At the same time, it is becoming evident that heterotrophic bacteria (but also cyanobacteria and unicellular eukaryotes, as discussed below) live and die in complex communities that in many ways resemble a multicellular organism (Lewis, 2000; Claessen *et al.*, 2014). In this regard, examples of cell-cell communication and RCD have been identified in heterotrophic bacteria (Engelberg-Kulka *et al.*, 2006). For example, *Bacillus subtilis* sporulating cells destroy their siblings and consume the nutrients thus liberated. An as-yet-unidentified extracellular killing factor mediates this cannibalism response, causing RCD and preventing sporulation of neighboring cells (González-Pastor *et al.*, 2003).

RCD has been documented in both cyanobacteria (prokaryotic) and eukaryotic phytoplankton (Berges and Choi, 2014; Bidle, 2016; Aguilera *et al.*, 2021). Eukaryotic phytoplankton are diverse and RCD has been best studied in green algae (mainly in chlorophytes, e.g., *Chlamydomonas* and *Volvox*), diatoms (e.g., *Thalassiosira*, *Phaeodactylum and Skeletonema*), dinoflagellates (e.g., *Peridinium*), and haptophytes (e.g., the coccolithophore *Emiliania huxleyi*) (Bidle, 2016; Desnitskiy, 2021; Barreto Filho *et al.*, 2022). Therefore, in an evolutionary context, RCD operates in independently evolving phytoplankton lineages including i) cyanobacteria, present in marine ecosystems for at least 2,600–2,300 Mya/2.6- 2.3 billion years (Sánchez-Baracaldo, 2015), ii) representatives of the green lineage which gave rise to land plants, and iii) diverse representatives of the red lineage, which after subsequent endosymbiotic events gave origin to several algal lineages (Fig. 1).

Phytoplankton presents several traits of multicellularity. While filamentous cyanobacteria represent true multicellular forms composed by different and mutually dependent cell types connected through septal junctions (Herrero *et al.*, 2016; Kieninger and Maldener, 2021), unicellular phytoplankton frequently resembles a multicellular community as opposed to a haphazard assembly of cells (Abada and Segev, 2018). Growing evidence suggests that phytoplankton dynamics are regulated at the population level through cell-cell communication (Bidle, 2016; Venuleo *et al.*, 2017;

Abada and Segev, 2018). Phytoplankton blooms, the massive proliferation of some phytoplankton in a short time both in fresh and marine water, represent a nice example of tight regulation and specific cell-cell communication (Glibert *et al.*, 2005). During bloom development and demise, phytoplankton is subjected to diverse environmental abiotic (e.g., nutrient deprivation, high light, and excess salinity) and biotic (grazers, viruses, and allelopathic interactions) stress conditions. These lead to the production of signaling molecules that mediate cell-cell communication and elicit a population-level response, ultimately shaping population dynamics (Hay, 2009; Saha *et al.*, 2019).

In the multicellular chlorophyte *Volvox carteri*, somatic cells undergo RCD as a final step of differentiation (Pommerville and Kochert, 1981; Desnitskiy, 2021). The task division between somatic and germline cells, which culminates in the death of a specific cell type, has led to studies on the evolution of multicellularity in the green lineage (Michod *et al.*, 2003). Indeed, RCD is considered an instrumental step in the evolution of multicellularity, since it allows conflict mediation between individual cells and the multicellular organism (Durand *et al.*, 2019). Therefore, considering the conservation of -survival and -death signals within the green lineage (Chlorophytes + Streptophytes) may provide an insight into the role of cell-cell communication in the evolution of multicellularity leading to vascular plants. Finally, RCD has also been described in macroalgae such as *Laminaria japonica* and *Saccarina japonica* (Wang *et al.*, 2004, 2013*b*). However, knowledge of the role of cell-cell communication during RCD in macroalgae is very scarce. In the following sections, we review cellular signaling molecules with pivotal functions in RCD induction and propagation in prokaryotic and eukaryotic phytoplankton, and their link in phytoplankton blooms when possible.

In vascular plants, cell-cell communication mediated by signaling molecules can be achieved through the symplastic (via plasmodesmata and vascular tissue) or apoplastic (extracellular) route. Recently, membrane-bound extracellular vesicles were identified in plants as an alternative route for signal spreading. In the following sections, we examine the role of symplastic and apoplastic signals, as well as extracellular vesicles in mediating cell-cell communication during RCD.

Extracellular ATP

Extracellular ATP (eATP) is a signaling molecule that participates in diverse physiological processes in vascular plants, including stomatal opening, pollen tube growth, gravitropism, wounding and response to pathogens (Tang *et al.*, 2003; Rieder and Neuhaus, 2011; Clark *et al.*, 2011; Lim *et al.*, 2014; Wang *et al.*, 2019). In vascular plants, eATP is secreted during anther dehiscence, stomatal movement, and even under unchallenged conditions (Jeter *et al.*, 2004; Chivasa *et al.*, 2005; Weerasinghe *et al.*, 2009; Rieder and Neuhaus, 2011; Clark *et al.*, 2011; Clark and Roux, 2018). Mechanical wounding, which leads to cell damage, results in eATP release in bean (*Phaseolus vulgaris*) and Arabidopsis, and similar results have been obtained with osmotic stress in Arabidopsis and *Populus eupharatica* (Jeter *et al.*, 2004; Song *et al.*, 2006; Sun *et al.*, 2012*b*; Wang *et al.*, 2019). Furthermore, treatment of a *Medicago truncatula* root hair culture with the fungal elicitor chitin resulted in increased eATP release (Weerasinghe *et al.*, 2009).

eATP has been assigned a survival role in mycotoxin-induced RCD in Arabidopsis. Fumonisin B1 (FB1), produced by the maize fungal pathogen *Fusarium verticilloides,* induces local and systemic RCD in Arabidopsis (Asai *et al.*, 2000; Stone *et al.*, 2000; Chivasa *et al.*, 2005). Interestingly, eATP depletion precedes FB1-induced RCD, and exogenous ATP rescues Arabidopsis from FB1-induced RCD (Chivasa *et al.*, 2005; Smith *et al.*, 2021). This indicates that changes in eATP concentration are tightly linked to pathogen-induced RCD. Importantly, the rescue was observed locally and in systemic leaves, reinforcing the concept of eATP-related “death signals” (Smith *et al.*, 2021). PLCL1, an extracellular phospholipase C, contributes to the systemic propagation of FB1-induced RCD in Arabidopsis (Smith *et al.*, 2021). Arabidopsis *plcl1* mutants displayed reduced FB1-triggered RCD propagation in the infiltrated leaves and limited RCD systemic spread (Smith *et al.*, 2021). How PLCL1 and eATP limit RCD propagation remains elusive. However, these results show that plant cells communicate during control of RCD propagation, and that eATP is an important pillar in this process.

Further evidence on eATP as a survival signal comes from cell suspensions of *Nicotiana tabacum* (tobacco) treated with SA (Feng *et al.*, 2015*a*,*b*). Treatment with SA caused a reduction in cell viability, which was alleviated by ATP. Furthermore, the effect of eATP on SA-induced RCD was abolished when Ca^{2+} uptake from the extracellular space was suppressed by the Ca^{2+} channel inhibitor $GdCl_3$ and the Ca^{2+} chelator EGTA. This suggests eATP may exert its survival role through an increase in Ca^{2+} influx from the extracellular space. Indeed, Ca^{2+} has previously been reported as a signaling molecule downstream of eATP perception (Demidchik *et al.*, 2009; Sueldo *et al.*, 2010). In a similar study, copper (Cu^{2+}) induced RCD in tobacco cell suspensions and wheat roots (Jia *et al.*, 2019). The authors used a chamber with compartments separated by semipermeable membrane to allow Cu^{2+} and ATP to diffuse, but not larger molecules (such as ATPase). Cells or wheat roots were treated with Cu^{2+} or Cu^{2+} and ATPase, and then incubated in one compartment of the chamber, while untreated cells or roots were placed in the other compartment. Untreated cells next to a compartment with Cu^{2+}-treated cells showed increased RCD compared to the control, and RCD was higher in the treatment Cu^{2+} + ATPase. In line with these findings, Cu^{2+}-induced RCD resulted in increased eATP in both the treated and untreated compartments, suggesting that tobacco cells and wheat roots secreted ATP during RCD (Jia *et al.*, 2019).

On the flip side of the coin, exogenous application of ATP triggers RCD. A cell suspension of *Populus euphratica* (poplar) treated with exogenous ATP displayed the typical characteristics of RCD in a Ca^{2+}-dependent manner – i.e., activation of caspase-like activities, cytochrome C release from the mitochondria and DNA fragmentation (Sun *et al.*, 2012*a*). This indicates that eATP can activate a RCD pathway in plants, with some similarities to what has been described in animals.

Arabidopsis plants exposed to cadmium (Cd^{2+}) experienced lipid peroxidation and RCD (Hou *et al.*, 2017). Cd^{2+} exposure also led to increased lipoxygenase activity, and several antioxidant enzymes including catalase, peroxidase, and superoxide dismutase, suggesting the initial production of lipoxygenase-derived molecules are then quenched. Remarkably, the *dorn1* mutant, which is

compromised in eATP perception, displayed reduced lipoxygenase, catalase, and superoxide dismutase activity, but increased lipid peroxidation. Furthermore, eATP in the apoplast increased upon Cd^{2+} treatment. These findings suggest that eATP participates in the response to Cd^{2+}, and that its perception is required to limit lipid peroxidation.

Exposure to the ATP analog AMP-PCP (ß-g-methyleneadenosine 5´-triphosphate) also induced macroscopic RCD in Arabidopsis and tobacco (Chivasa *et al.*, 2005). Since AMP-PCP mimics ATP but cannot be hydrolysed by endogenous nucleases, it potentiates responses linked to eATP perception. However, non-hydrolysable ATP analogs may also act as competitive inhibitors of apoplastic enzymes that use ATP as a substrate (Chivasa *et al.*, 2009). Therefore, this dual effect might provide a technical explanation to the contrasting effects in RCD when apoplastic eATP is manipulated. Importantly, these results confirm previous observations showing that there is an optimal eATP concentration for life (Clark and Roux, 2018).

The findings discussed here indicate eATP participates in plant RCD and that eATP acts as a death and as a survival signal upon different scenarios. Furthermore, manipulation of eATP in the apoplast can lead to systemic RCD, hinting at the moving nature of plant RCD (Chivasa *et al.*, 2009; Smith *et al.*, 2021). Therefore, both increased and decreased eATP concentration can lead to compromised cell viability. Although it is still challenging to interpret this data, it provides evidence that cells engage in cellular communication during RCD. An important point to address is whether loss of cell viability is the result of the induction of a RCD program. In other words, does eATP induce RCD in all cases, or can cell death be the result of accidental necrosis due to limited or excess of ATP? Diving deeper into the signaling cascade associated with eATP-cell death will help unravel this question. Similarly, combining different ATP non-hydrolysable agonists with mutants impaired in eATP perception will help discriminating eATP perception-dependent from eATP hydrolysis-dependent processes in the apoplast. Efforts should be increased to expand the identification of eATP receptors

in more photosynthetic species. This will allow addressing the mechanism by which eATP contributes to the control of RCD propagation in the green lineage, which is still obscure.

eATP perception is conserved amongst photosynthetic organisms beyond vascular plants. In the seaweed *Mazzaella laminarioides* (Rhodophyte), eATP and other purines influence spore motility, congregation and coalescence in a dose-dependent manner, and high eATP concentration induce spore death (Huidobro-Toro *et al.*, 2015). Furthermore, mild shaking induced eATP secretion from thalli of *M. laminariodies*, suggesting eATP might be involved in cell-cell communication during wounding induced-cell damage (Huidobro-Toro *et al.*, 2015). eATP perception has also been observed in unicellular green algae and macroalgae. In the green macroalgae *Dasycladus vermicularis* and *Acetabularia acetabulum,* eATP perception leads to nitric oxide (NO) and reactive oxygen species (ROS) production, whereas wounding-induced ROS and NO production is inhibited by the purinoreceptor antagonist PPADS (Torres *et al.*, 2008). These findings indicate that eATP is released by wounded macroalgae cells, and that eATP perception in macroalgae is mediated by a purinoreceptor-like protein (Torres *et al.*, 2008). Similarly, the genome of the single-celled green algae *Ostreococcus tauri* has four sequences with homology to P2X, one the human eATP receptor families (Fountain *et al.*, 2008). Heterologous expression and characterisation revealed that *Ot*P2X partially localizes to the plasma membrane and induces ATP-dependent inward current in HEK293 cells, which normally do not respond to eATP (Fountain *et al.*, 2008). Though the evidence is still limited to a few species and our understanding of the physiology of eATP signalling in Chlorophytes and other algae is scarce, these findings show eATP perception and release to the extracellular space upon wounding is conserved in eukaryotic photosynthetic organisms. Given the conserved role of eATP in cell-cell communication during RCD in animals and plants, it is tempting to speculate that a similar function is fulfilled in algae.

Extracellular peptides

Small peptides (<100 amino acids) participate in a wide range of cellular functions in all kingdoms (Sousa and Farkas, 2018; Fabre *et al.*, 2021). Cyanobacteria and microalgae produce a large diversity of peptides, though research has mainly focussed on their characterization as antibacterial, antitumoral or others biotechnological traits (Rojas *et al.*, 2020). Among cyanobacterial secondary metabolites, microcystins are a group of cyclic hepatotoxic heptapeptides produced by several genera that have received special attention as they pose an ecotoxicological and sanitary risk worldwide (Svirčev *et al.*, 2019). Microcystins are typically intracellular metabolites, but their extracellular multifunctional traits have been gradually recognized, for example in cell–cell communication (Schatz *et al.*, 2007). In this sense, a conceptual model coupling RCD and extracellular microcystins have been proposed for *Microcystis* (Hu and Rzymski, 2019), the most common bloom-forming cyanobacteria in freshwater ecosystems (Harke *et al.*, 2016; Svirčev *et al.*, 2019). During stress response and RCD, microcystins are released from some cells within the colony into the extracellular environment. Extracellular microcystins increase the production of extracellular polysaccharides that are involved in colony formation, thus improving the survival of the remaining cells under stressful conditions (Gan *et al.*, 2012; Hu and Rzymski, 2019). Taken together, these findings would point to the role of extracellular microcystins as survival signals.

Plant peptides can be synthesized from a protein precursor or can be encoded by short open reading frames (SORFs) (Tavormina *et al.*, 2015; de Bang *et al.*, 2017; Lyapina *et al.*, 2021). Recent reviews address peptide biosynthesis, activity, and function, and the technologies used to study such a complex world (Stührwohldt and Schaller, 2018; Chen *et al.*, 2020; Kim *et al.*, 2021). There are numerous examples of peptide-mediated growth regulation, development and stress response

(Murphy *et al.*, 2012; Vitorino *et al.*, 2021), but evidence on their role in RCD regulation is is only just starting to emerge (Table 1).

Developmental RCD (Box 1) provides a clear example where death must be restricted to a specific cell and prevented in adjacent ones. During tracheary elements (TE) differentiation at least two functional peptides are secreted, Kratos and Bia, providing good evidence of how RCD communication may operate (Escamez *et al.*, 2019). Kratos is released from TE cells preventing RCD in neighboring non-tracheary element cells. Furthermore, Kratos infiltration into Arabidopsis leaves reduces RCD induced by abiotic stress. In contrast, Bia enhances mechanical stress-induced RCD, although it has no effect on increasing developmental RCD (Escamez *et al.*, 2019). The activity of cytosolic metacaspase 9 (MC9) is required to regulate Kratos and Bia in Arabidopsis, although protein precursors of both peptides are not direct targets of MC9. Since MC9 regulates autophagy flux during TE development, Kratos and Bias could be regulated through MC9-modulation of autophagic flux (Escamez *et al.*, 2019). Thus, protein and peptide secretion in plants may depend on autophagy, similar to what happens during RCD caused by inflammation in metazoans (Escamez *et al.*, 2019).

GRI (Grim Reaper) is another example of a peptide that induces RCD (Wrzaczek *et al.*, 2009, 2015) and could be involved in cell-cell communication. GRI was identified in Arabidopsis and is produced through direct processing of GRI precursor protein by extracellular MC9. Upon infiltration in Arabidopsis, GRI binds to a plasma membrane-localized receptor (PRK5), inducing ROS-dependent RCD (Wrzaczek *et al.*, 2015). Thus, only cells expressing PRK5 would die, making this a good system to strictly confine RCD. Interestingly, GRI protein has more than two cleavage sites recognized by MC9; thus more than one peptide can be produced, potentially with antagonists functions (Wrzaczek *et al.*, 2015). Similar mechanisms were described previously reported for CLAVATA3/ESR-RELATED 18, from which two different peptides with probably antagonistic functions (Murphy *et al.*, 2012).

KOD (kiss of death) is so far the only peptide encoded by a SORFs that has been involved in RCD (Blanvillain *et al.*, 2011; Fesenko *et al.*, 2019). Biotic and abiotic stress induce KOD expression, causing caspase-like activity and mitochondria misfunction-dependent RCD (Blanvillain *et al.*, 2011). Also, Arabidopsis *kod* mutants show reduced RCD of the embryo suspensor cells, pointing out a potential role for KOD in developmental RCD (Blanvillain *et al.*, 2011). There is yet no evidence of KOD movement, thus its role in cell-cell communication remains elusive.

The evidence described here supports a role for peptides as either survival or death molecules in plants and cyanobacteria. However, the peptides identified so far are limited, given the high number and diversity of peptides, proteases, and membrane receptors, it is conceivable that other already characterized and uncharacterized peptides mediate RCD propagation.

Extracellular Calcium

Several environmental factors trigger cytosolic increase of Ca^{2+} in photosynthetic organisms, leading to induction of RCD upon stress and development (Takabatake *et al.*, 2007; Clapham, 2007; Vardi, 2008; Ren *et al.*, 2021).

In vascular plants, Ca^{2+} fluxes occur via plasmodesmata, vascular tissues and apoplastic (extracellular) routes (Steinhorst and Kudla, 2014; Choi *et al.*, 2017; Toyota *et al.*, 2018). Several processes related to RCD involve systemic long-distance transmission of Ca^{2+}. There is now also evidence for the systemic spread of a Ca^{2+} as waves that couple local sensing of stimuli like wounding or abiotic stress to plant-wide adaptive responses (Choi *et al.*, 2014; Gilroy *et al.*, 2016). Calcium elevation is a critical step in plant innate immunity. Pathogen perception is translated into elevated intracellular Ca^{2+} (iCa^{2+}) (mediated by plasma membrane and intracellular channels) as an early step in the signaling cascade (Ma and Berkowitz, 2007). This iCa^{2+} elevation is mainly mediated by an increase in Ca^{2+} influx from the apoplast (Ma and Berkowitz, 2007)

In systemic RCD (Box 2), Ca^{2+} likely acts as a death signal. An increase in Ca^{2+} is observed at the root tip one day post inoculation (1dpi) of tomato leaves with Tobacco mosaic virus (TMV), with ROS accumulating in the root-tip cells at 5dpi. Elevated Ca^{2+} at the root tip continue until the 15dpi. Finally, at 20 dpi, root tips showed RCD (Li *et al.*, 2018). The underlying physiological mechanisms of systemic RCD are poorly understood, and how Ca^{2+} waves - and other molecules- are involved in the RCD signal transmission from leaf to root remains to be elucidated.

External addition of Ca^{2+} induces RCD in cell cultures of *Alyssum inflatum* (Ghasemi *et al.*, 2020). Several experiments suggest the role of extracellular Ca^{2+} (eCa^{2+}) as a signal molecule promoting RCD. The $eCa2^{+}$ chelator EGTA blocks ferroptosis in Arabidopsis roots (Distéfano *et al.*, 2017). Inhibition of Ca^{2+} influx , with the Ca^{2+} channel-blocker lanthanum chloride ($LaCl_3$), prevented RCD in Arabidopsis suspension cultures exposed to ceramides (Townley *et al.*, 2005) and in the rice root tip challenged by salt stress (Li et al. 2007).

Recent work performed in Arabidopsis root cells damaged by multiphoton laser shows that cytosol-localized PRECURSOR OF PEP1 (PROPEP1) and METACASPASE4 (MC4) react only after the loss of plasma membrane integrity and prolonged eCa^{2+} entry. Ca^{2+} mainly originates from the extracellular space and potentially from vacuole, activating Ca^{2+}-dependent MC4 to cleave PROPEP1. PEP1 is released from the tonoplast into the cytosol, from where it can passively diffuse (or potentially actively secreted) through the compromised plasma membrane to bind the membrane-localized BAK1-PEPR1/2 receptor kinase complex, inducing RCD activation in the surrounding intact cells. These results suggest direct evidence of eCa^{2+} as a regulator in RCD of damaged cells of plants (Hander *et al.*, 2019).

Upon sensing of wounding by herbivore attack or mechanical damage, plant cells transmit systemic signals activating defense responses in undamaged parts (referred to as systemic wound response SWR, Box 2). Glutamate released after wounding is perceived by glutamate receptor–like ion channels that convert this signal into an increase in $iCa2^{+}$ concentration, which propagates to distant

organs, inducing an immune response. Transmission of Ca^{2+} takes place through the phloem and plasmodesmata (Toyota *et al.*, 2018). Therefore, Ca^{2+} acts as a death signal for the damaged cells and survival signal to the undamaged cells that activate a defense response.

Phytoplankton live in environments where Ca^{2+} ions can reach 10 mmol L^{-1}, while free Ca^{2+} in the cytosol is maintained at ~ 0.1 µmol L^{-1} (Müller *et al.*, 2015). Upon stress, transient Ca^{2+} increases go in hand with ROS or NO) production (Vardi *et al.*, 2006; Agostoni and Montgomery, 2014). Furthermore, exogenous Ca^{2+} supplementation improves the tolerance to heat stress in the cyanobacteria *Anabaena* sp. PCC 7120 and prevents RCD in *Synechocystis* sp. PCC 6803, suggesting a role for Ca^{2+} in maintaining cell viability under abiotic stress (Tiwari *et al.*, 2016; Aguilera *et al.*, 2022). Still, there is limited evidence for Ca^{2+} as an extracellular molecule mediating cell-cell communication and RCD in phytoplankton. Considering its conserved role in RCD in metazoans and vascular plants, it would be interesting to investigate a potential function for Ca^{2+} in mediating cell-cell communication during RCD in this group.

ROS

Reactive oxygen species are chemical species produced upon electron transfer to oxygen (hydrogen peroxide, H_2O_2; superoxide, O_2^-; hydroxyl radical superoxide, OH−; and hydroxyl radicals). In photosynthetic organisms, ROS are a byproduct of respiration and photosynthesis and are mainly generated in the thylakoid membranes (cyanobacteria), cellular compartments such as chloroplasts, mitochondria, and peroxisomes (eukaryotic phytoplankton and plants), and on the cell surface (eukaryotic phytoplankton and vascular plants) (Schmitt *et al.*, 2014; Diaz and Plummer, 2018). The over accumulation of ROS damages organelles and important biomolecules leading to cellular injury and RCD (Schmitt *et al.*, 2014; Mittler, 2017). However, ROS are also key players in physiological processes such as cell differentiation and proliferation, and serve as important signals during

acclimation to stress conditions and RCD (Jauzein and Erdner, 2013; Schmitt *et al.*, 2014; van Creveld *et al.*, 2015; Bidle, 2016; Mittler, 2017; Mizrachi *et al.*, 2019; Aguilera *et al.*, 2021). Moreover, ROS molecules can generate further oxidation products (e.g., lipoperoxides) that are also involved in signaling pathways. All this supports the dual role of intracellular ROS as survival death signals in photosynthetic organisms, depending on different levels of reactivity, sites of production and potential to cross biological membranes (Mittler, 2017; Huang *et al.*, 2019).

Extracellular ROS (eROS) can occur naturally in aquatic environment as the result of both non-biological and biological chemical reactions. Several eukaryotic phytoplankton and cyanobacteria produce eROS (in particular H_2O_2, O_2^-) under optimal growth conditions in culture (Diaz and Plummer, 2018; Sutherland *et al.*, 2019). The majority of these are bloom-forming species, potentially linking eROS production with bloom formation (Diaz and Plummer, 2018). In eukaryotic phytoplankton, O_2^- is produced extracellularly, mainly by cell surface NADPH oxidases (Kim *et al.*, 2007; Diaz *et al.*, 2019). On other hand, eROS have been implicated in survival functions related to iron acquisition, cell growth and proliferation, as well as in modulation of biological interactions such as grazing and viral infection (Diaz and Plummer, 2018). Furthermore, ROS -in particular O_2^- - was proposed to mediate cell-cell communication and transmit information on cell density in bloom forming species (Marshall *et al.*, 2005; Hansel *et al.*, 2016). During cyanobacterial blooms, the production of ROS can be substantial and influence the structure and function of the photoautotrophic community (Cory *et al.*, 2016).

eROS production has also been observed in green, brown, and red macroalgae and associated to development and response to biotic and abiotic stress (for a recent comprehensive review see Hansel and Diaz, 2021). In the red algae *Glacilaria conferta*, treatment with cell wall fragments lead to production of eROS, likely through the activity of a plasma membrane-localised NADPH oxidase, as described for vascular plants (Weinberger *et al.*, 2005; Torres *et al.*, 2005). Similarly, eROS have also been described upon wounding in *Euchema platycladum* (Collén *et al.*, 1994). However, in these

examples, a role for eROS in mediating cell-cell communication during RCD in macroalgae remains to be addressed.

In vascular plants, ROS play a central role in response to abiotic stress, pathogen attack and wounding, as well as during development (Mittler *et al.*, 2011; Schmitt *et al.*, 2014; Mittler, 2017). In addition to triggering responses at the site directly exposed to the stress, ROS regulate rapid systemic responses in the whole plant such as the systemic acquired acclimation (SAA), the systemic acquired resistance (SAR), and the systemic wound response (SWR) (Box 2).

The respiratory burst oxidase homolog genes D and F (*RBOHD* and *RBOHF*) participate in the apoplastic ROS burst induced in Arabidopsis upon infection with *Pseudomonas syringae* DC3000 expressing *AvrRpm1.* The ROS burst is abolished in the *rbohD* single mutant and the *rbohD/rbohF* double mutant, but not in the *rbhoF* single mutant, suggesting RBOHD plays a major role in eROS production (Torres *et al.*, 2002). Activation of RCD was also affected in these mutants, as both the double mutant and *rbohF* showed less RCD, supporting a death role RBOH-derived ROS. These findings suggest a strong participation of RBOHD in the ROS burst, whereas RBOHF appears to be involved in RCD activation (Torres *et al.*, 2002).The different roles of RBOHD and RBOHF in controlling ROS burst and RCD activation and propagation probably reflect specific spatiotemporal regulation of their activities.

In a follow-up study, the role of RBOH-derived ROS burst in RCD propagation was further investigated (Torres *et al.*, 2005). Arabidopsis LSD1 is a zinc-finger protein that negatively regulates RCD propagation to uninfected cells (Dietrich *et al.*, 1997). Therefore, the *lsd1* mutant cannot control RCD spread, resulting in runaway RCD from the initial activation site. This runaway RCD can be triggered by O_2^- and by SA (Jabs *et al.*, 1996). RCD induced in the *lsd1* mutant by SA was restricted to the treated leaf. However, RCD in the double mutants *lsd1 rbohd* and *lsd1 rbohf* spread beyond the treated leaf and became systemic. This indicates that ROS produced by RBOHD and RBOHF acts a as a survival signal limiting systemic spread of SA-induced RCD (Torres *et al.*, 2005).

The different roles of RBOHD and RBOHF in controlling ROS burst and RCD activation and propagation probably reflect specific spatiotemporal regulation of their activities. Furthermore, ROS derived from RBOHF acts as death or survival signals depending on the pathogen and the strength of the immune response (Torres *et al.*, 2005).This result stresses the importance of investigating multiple pathogens, as their distinct immune responses they trigger may induce specific survival or death signals.

Oxidized lipids and lipid-derived molecules

Oxylipins are derived from the oxidative metabolism of poly-unsaturated fatty acids via enzymatic and non-enzymatic pathways, and are involved in RCD induction (Wasternack and Feussner, 2018; Mehta *et al.*, 2021). Oxylipins have been reported in several photosynthetic organisms, including cyanobacteria (Wasternack and Feussner, 2018; Aguilera *et al.*, 2022), diatoms (D'Ippolito *et al.*, 2009; Gallina *et al.*, 2016), dinoflagellates (Dorantes-Aranda *et al.*, 2009), raphidophytes (Giner *et al.*, 2008) and vascular plants (Wasternack and Feussner, 2018). While cyanobacteria produce only simple oxylipins, eukaryotic phytoplankton and plants have evolved complex pathways leading to different molecules (Wasternack and Feussner, 2018).

In phytoplankton, oxylipins have been extensively investigated for their deleterious effects on grazers and hemolytic activities (Ianora *et al.*, 2004; Dorantes-Aranda *et al.*, 2009). However, it is now evident that they also mediate phytoplankton dynamics and interactions (Casotti *et al.*, 2005; Vardi *et al.*, 2006; van Creveld *et al.*, 2015). Oxylipins can be produced in large amounts upon wounding during grazing (Pohnert, 2000), but can also be released from intact microalgal cells (Vidoudez and Pohnert, 2008). Laboratory studies with the diatom *Skeletonema marinoi* further support the characterization of oxylipins as death/life signals, showing that both production and

effect of oxylipins are dependent on physiological state of cells, mainly nutrient status and age (Ribalet *et al.*, 2007; Vidoudez and Pohnert, 2008).

A common oxylipin produced by marine diatoms, the polyunsaturated aldehyde (2E,4E/Z)-decadienal (DD), strongly impacts grazers reproduction (Ianora *et al.*, 2004) and diatoms themselves. DD regulates intercellular signaling and monitors stress levels, and it has both survival and death functions depending on the released concentration (Casotti *et al.*, 2005; Vardi *et al.*, 2006). In *Thalassiosira weissflogii,* DD-like aldehydes released in the water trigger a stress response leading to Ca^{2+}- and NO- dependent RCD in surrounding cells (Casotti *et al.*, 2005). In *Phaeodactylum tricornutum*, DD perception similarly leads to Ca^{2+} and NO signaling, and the integration of these intracellular signals determines cell fate (Vardi *et al.*, 2006). Such death mechanisms, acting in cell-cell interactions within diatom populations, could regulate the synchronization of bloom demise (Vardi *et al.*, 2006; D'Ippolito *et al.*, 2009). Interestingly, from a survival point-of-view, the pretreatment of cells with sublethal doses of DD initiates an intracellular signaling cascade, also involving Ca^{2+} and NO, that immunizes cells against subsequent lethal concentrations of DD (Vardi *et al.*, 2006) (Figure 2B). This adaptive response could increase the chance of survival for a part of the population in a decaying or highly grazed bloom.

Recently, sulfate-containing lipids such as sterol sulfates have been suggested to have a similar death role as oxylipins in marine diatoms (Gallo *et al.*, 2017). Three major active sterols (β-sitosterol sulfate, dihydrobrassicasterol sulfate and cholesterol sulfate) accumulate in senescent cells of *Skeletonema marinoi*. When exposed to the sterol sulfates, intracellular ROS and NO increased in *S. marinoi* cells leading to growth arrest or RCD depending on the dose. Thus, as for some oxylipins, these small metabolites could have an active role in regulating bloom dynamics and demise (Gallo *et al.*, 2017).

Massive blooms of coccolithophore *Emiliania huxleyi* (haptophyte) are routinely infected and terminated by lytic Coccolithoviruses (Bratbak *et al.*, 1993; Vardi *et al.*, 2009, 2012). Upon infection

of natural populations, coccolithoviruses-derived glycosphingolipids accumulate in infected cells and trigger the production of ROS, NO, and caspase-specific activity in *E. huxleyi* leading to RCD. In addition, purified viral glycosphingolipids also induce biochemical hallmarks of RCD in uninfected cells in a dose-dependent manner (Vardi *et al.*, 2009, 2012). The induction of RCD in both infected and uninfected cells of *E. huxleyi* could limit production and propagation of viruses (Vardi *et al.*, 2009; Bidle, 2016). In such biotic interactions, a death signal at the cellular scale becomes survival at the population scale.

Plant oxylipins are antibacterial agents. Volatile phyto-oxylipins are produced by wounded plant tissues during defense (Bleé 2002), as described in phytoplankton (Pohnert, 2000). Methyl jasmonate (Me-JA) is volatile and can diffuse between cells, triggering different responses including RCD. A complete review of JA-derived oxylipins as mediators of plant–pathogen interaction was recently published. A complete review of JA-derived oxylipins as mediators of plant–pathogen interaction was recently published (Mehta *et al.*, 2021). Oxophytodienoic acid (OPDA), hydroxides, triols, ketones, epoxides, ketols, and the JA group, are implicated as communication signals in tomato–root-knot nematode (*Meloidogyne javanica*) interaction (Fitoussi *et al.*, 2021).

JA and Me-JA have been implicated as signals involved in RCD communication induced by abiotic stress (temperature, radiation, nutrients) and leaf senescence. They repress the synthesis of photosynthetic proteins, causing a drastic drop in photosynthesis and carbon dioxide fixation, which results in the induction of leaf senescence (Baldwin *et al.*, 2006; Reinbothe *et al.*, 2009). After Me-JA treatment, ROS induction in mitochondria and chloroplasts, leads to photosynthetic dysfunction and subsequent RCD (Zhang and Xing, 2008). Under senescent conditions, membrane fatty acid peroxidation would predominate and initiate regulated organelle destruction (Reinbothe *et al.*, 2009). Therefore, oxylipins might

act in cell-cell communication during RCD in damaged tissues due to biotic and abiotic stresses.

Extracellular nitric oxide

NO, a gaseous, highly reactive radical, is an intra- and extracellular messenger that mediates diverse signaling pathways across all kingdoms of life (Tuteja *et al.*, 2004; Jeandroz *et al.*, 2016; Astier *et al.*, 2021). NO is synthesized enzymatically by nitric oxide synthase or nitrate reductase and non-enzymatically from nitrite in acidic compartments such as the apoplast of plant cells (Yamasaki *et al.*, 1999; Jeandroz *et al.*, 2016). Once produced, NO readily crosses membranes by simple diffusion triggering a multitude of responses in the surrounding cells. NO stands as a key signaling molecule involved in development, cell-cell communication, stress surveillance, and RCD in photosynthetic organisms (Bidle, 2016; Jeandroz *et al.*, 2016; Astier *et al.*, 2021).

In open oceans, NO was originally associated with nitrite photolysis and bacterial denitrification and nitrification processes without a precise biological function (Ward and Zafiriou, 1988; Galluzzi *et al.*, 2018). However, extracellular NO (eNO) is also produced by photosynthetic microorganisms and may act as a signal that spreads through the cell population triggering RCD or a survival message in neighboring cells. The ability of NO to act as a diffusible extracellular signal in aquatic environments was first proposed in diatoms (*T. weissflogii* and *P. tricornutum*) where it is a critical component of stress perception, possibly triggering RCD in neighboring cells (Vardi *et al.*, 2006, 2008). In cultures of the marine alga *E. huxleyi,* intracellular NO production was detected 24 h after viral infection (Schieler *et al.*, 2019) and before ROS burst, which appears to be required for RCD induction and host cell lysis (Sheyn *et al.*, 2016). Moreover, eNO was also detected in the cell-free media after infection and was proposed to function as a signal, communicating infection to neighboring cells (Schieler *et al.*, 2019)

Furthermore, co-cultivation of *E. huxleyi* with the aerobic bacterium *Phaeobacter inhibens* triggers RCD in the algal population (Abada *et al.*, 2021). *E. huxleyi* secretes nitrite to the culture media during exponential growth, while *P. inhibens* reduces nitrite to NO through denitrification. Interestingly, NO production and RCD were abolished when the alga was co-cultured with a *P. inhibens* strain mutated in denitrification genes (e.g., nirK). Therefore, this suggests that eNO produced by bacteria-mediated denitrification can diffuse to induce E. *huxleyi* RCD. Indeed, the authors suggested that inorganic nitrogen exchange between bacteria and photosynthetic microorganisms is an ecologically significant microbial communication across kingdoms (Abada *et al.*, 2021). Likewise, eNO has been implicated in the response of *Chlorella vulgaris* to Cu^{2+} stress, protection of *Scenedesmus obliquus* against H_2O_2, and reduction of UV-B damage in the cyanobacterium *Spirulina platensi* (Astier *et al.*, 2021). Whether NO spreads through the aqueous solution in these cases acting as a cell death/survival molecule remains elusive.

In plants, NO has a survival role by acting both as a protection against RCD and as an antioxidant molecule diminishing ROS levels. Paradoxically, in some cases, NO can be cytotoxic, resulting in RCD. These cytotoxic and protective functions are often dependent on the NO concentration (Beligni and Lamattina, 1999). eNO also plays a role in cell-cell communication in vascular plants. Aleurone cell layers, a secretory tissue that surrounds the starchy endosperm and embryo in barley, release NO under aerobic conditions (Vitecek *et al.*, 2008). Gibberellins (GAs) trigger the synthesis and secretion of **α**-amylase and other hydrolytic enzymes that provide nutrients for the growing embryo. Following GA-induced enzyme secretion, the aleurone layer undergoes ROS burst and RCD (Bethke and Jones, 2001; Fath *et al.*, 2001). GA also induces non-enzymatic NO production in the apoplast of barley aleurone cells (Bethke *et al.*, 2004). Curiously, exogenous application of NO delayed RCD in aleurone cells treated with GA by increasing their capacity to metabolize ROS. The

NO effect is specific since it has no effect on GA-induced secretion of hydrolytic enzymes (Beligni *et al.*, 2002). These results indicate that NO produced by aleurone cells in barley acts as a regulator of RCD exerting a protective and antioxidant role, possibly for the growing embryo. The role of eNO in the aleurone layer as a cell-to-cell signal in seeds needs to be explored.

The role of NO during plant defense responses has also received attention. Tobacco cells exposed to the elicitor cryptogein show a burst in NO detected in the cellular medium (Besson-Bard *et al.*, 2008; Vitecek *et al.*, 2008). The hypersensitive response (HR) is a well-known process in all higher plants characterized by rapid RCD surrounding the pathogen-infection site. NO acts synergistically with ROS to potentiate the induction of HR-RCD upon pathogen challenge (Delledonne, 2005; Laxalt *et al.*, 2007). First evidence that NO may contribute to cell-cell communication during HR comes from Arabidopsis plants infected with *Pseudomonas siringae* expressing the effectors *avrB* or *avrRpt2*. Kinetics of NO accumulation appeared closely parallel to HR progression. Since NO was detected intra and extracellularly, authors speculate that NO functions as a spreading signal communicating the HR process in plants (Zhang et al 2003).Later studies in Arabidopsis using S-nitrosoglutathione reductase (*gsnor*) mutants indicate that NO positively regulates HR-RCD. However, NO also triggers a feedback loop limiting the HR by the inhibition of RBOHD activity through S-nitrosylation (see ROS section), abolishing ROS production (Yun et al. 2011). Therefore, this suggests that NO may act in cell-cell communication to inhibit RCD signaling in the leaf tissue and restrain the HR response.

Other signaling molecules in mediating communication and RCD in phytoplankton

While ROS and NO are general death/survival signals and shared across kingdoms, others are more specific to a single group of organisms. In this section, we briefly review a series of signaling molecules that specifically mediate phytoplankton interactions and have recently received increased attention.

Phytoplankton demise through RCD influences the flow and fate of photosynthetically fixed organic matter in aquatic systems (Bidle, 2016). The dissolved organic matter (DOM) comprises various organic compounds and amino acids that are assimilated and re-mineralized by other organisms either within the same population, or by other prokaryotes and protozoa (Bidle, 2016; Durand *et al.*, 2016). These released compounds are signals that affect surrounding cells and their survival. In the chlorophyte *Dunalliela salina*, RCD causes the release of organic nutrients such as glycerol, which can be used by other individuals of the same species or others, like *Halobacterium salinarum*, a co-occurring halophilic archaeon (Orellana *et al.*, 2013).. Similarly, the growth of the dinoflagellate *Alexandrium minutum* can be stimulated by the release of DOM from dead individuals of the same species or closely related ones (other species of the same genus) (Lu et al. 2016; Brown and Kubanek 2020). In the chlorophyte *C. reinhardtii*, how cells die directly impacts the fitness of their neighbors (Durand *et al.*, 2011). During RCD, unidentified thermostable molecules released by *C. reinhardtii* promote survival of neighboring cells of the same species. However, when *C. reinhardtii* cells dye by ACD (accidental cell death, non-RCD) they release molecules that are harmful to neighboring individuals of the same species, suggesting different cell death mechanisms (RCD vs ACD) affect population dynamics differently (Durand *et al.*, 2011).

Plasmodesmata as cellular gate keepers restricting /spreading death signals

In human cells, Gap Junction Channels connect neighboring cells allowing a two-way exchange of death and survival signals (Krysko *et al.*, 2005). In fact, certain cells can "kill" the adjacent ones through such junctions, an effect known as the "bystander cell death" or "kiss of death" (Decrock *et al.*, 2009). In spite of the presence of a rigid cell wall, neighboring plant cells are also interconnected (Raven, 1997; Brunkard and Zambryski, 2017). In land plants most cells present plasmodesmata (PD), projections of the plasma membrane that interconnect adjoining cells, thus creating a symplastic continuum within tissues, organs, or the whole organism (Tilsner *et al.*, 2016; Li *et al.*, 2021). PD from vascular plants are traversed by strands of endoplasmic reticulum, called desmotubules (Sager and Lee, 2018), and have been demonstrated to represent crucial signaling hubs for the spatiotemporal regulation of different developmental and stress related pathways that might involve RCD (Sager and Lee, 2012). For instance, PD regulate the cell-cell flux of nutrients, hormones, proteins, RNAs, viruses and other foreign compounds (White and Barton, 2011; Burch-Smith *et al.*, 2011). Their highly dynamic structure, frequency and connectivity allow modulation of cell communication and isolation. This is necessary to regulate cell fate and for rapid responses to external stimuli (Sager and Lee, 2014; Godel-Jedrychowska *et al.*, 2020).

Adjustments in PD dynamics accompany the execution of many differentiation programs, some of which lead to RCD. For instance, PD degeneration is required for pollen development as it allows the separation of tapetal cells from the middle layer before these cells undergo RCD (Niu *et al.*, 2013). During leaf abscission, PD number and branching increase at the proximal side of the fracture zone, along with hallmark features of RCD (e.g., DNA fragmentation, increased levels of nuclease activity, expression of RCD-related genes) (Bar-Dror *et al.*, 2011). The root cap is characterized by high RCD rate, and a balance between cell division and cell death shapes root size and architecture (Fendrych *et al.*, 2014). Interestingly, while the outermost cells show decreased PD frequency and become

sealed prior to RCD, the PD in the inner cells remain permeable up until protoplasts condensate and shrink, suggesting PD functionality is associated to RCD in the root cap (Zhu and Rost, 2000).

PD permeability is regulated by proteins located within the PD and the plasma membrane. These proteins, in concert with Ca^{2+} and ROS fluxes, act as crucial regulators of the plasmodesmal pore size (Sager and Lee, 2014). In turn, PD connectivity modulates the spreading of local and long-distance signals. Integrative responses to biotic and abiotic stimuli, such as SAR, SAA and SWR rely on a central mechanism of PD gating (Box 2). Briefly, this gate mechanism requires plasmodesmata-localized protein 5 (PDLP5) and RBOHD-mediated oxidative burst, to promote wave-like propagation patterns (Lim *et al.*, 2016; Fichman *et al.*, 2021). Besides PDLP5, many other receptor-like proteins relocate from the plasma membrane to the PD upon ligand recognition, and induce callose deposition to restrict signal sharing between cells (Vu *et al.*, 2020; Cheval *et al.*, 2020).

PD closure plays a crucial role restraining RCD in response to pathogen infections. The HR is characterized by rapid RCD at the infection site, isolating the area from the uninfected surrounding cells, thus preventing the spread of the infection (Wang *et al.*, 2013*a*) (Box 2). PDLP5-mediated callose deposition in a SA-dependent process results in PD closure and the concomitant cell confinement (Lee *et al.*, 2011). Before their confinement, cells committed to die might signal the surrounding healthy cells through PD (as a burst of ROS intermediates), priming them for subsequent infections.

Early land plants and aquatic multicellular photosynthetic organisms also show cell-cell connections through PD and PD-like structures with different degree of complexity (Raven, 1997). In bryophytes, the moss *Physcomitrium patens* has become a model species for PD studies (Falz and Müller-Schüssele, 2019; Pfeifer *et al.*, 2022). *P. patens* cells develop PD that show certain degree of structural and functional conservation with Arabidopsis (Johnston *et al.*, 2022), although no apparent PDLP5 orthologous has been identified in the moss (Brunkard and Zambryski, 2017). Callose deposition and SAR-like responses (constrained to adjacent cells) take place in *P. patens*

exposed to different stresses (Carella and Schornack, 2018; Muller *et al.*, 2022). ROS burst and SA induction, the molecular signature of RCD in vascular plants, is also triggered in moss by *Botrytis* infection (Ponce De León *et al.*, 2012).

Besides the central role of SA, abscisic acid (ABA) seems to be the key hormonal regulator of PD mediated cell-cell communication in *P. patens* upon abiotic stress (Kitagawa *et al.*, 2019). Under adverse environmental conditions, or ABA stimulation, cells from the vegetative body of the moss can develop resistant structures, diaspores, while the adjacent cells, tmema, undergo RCD, serving as predetermined breaking points (Arif *et al.*, 2019; Falz and Müller-Schüssele, 2019). This mechanism resembles RCD associated to cell-cell separation processes such as leaf abscission or dehiscence in higher plants. Diaspores formation and tmema RCD require cell reprogramming (Sato *et al.*, 2017; Kubo *et al.*, 2019; Gu *et al.*, 2020). This process might also involve an ancient death signal, albeit evidence is lacking.

In aquatic environments, members of diverse algal lineages show different types of cytoplasmic bridges, from PD in brown algae to more rudimentary structures called pit connections in red algae (Raven, 1997; Kim *et al.*, 2022; Chaigne and Brunet, 2022). PD in multiseriate brown algae are line channels without desmotubules, usually clustered in specific areas (Terauchi *et al.*, 2015). Besides participating in intercellular translocation of molecules (Nagasato *et al.*, 2017) these PD also mediate wound signal propagation and H_2O_2 generation in response to cell damage (Tanaka *et al.*, 2017), that might also involve RCD.

Within photosynthetic prokaryotes, filamentous cyanobacteria develop gated septal junctions (SJ) functionally analogous to eukaryotic PD (Flores *et al.*, 2018). Under unfavorable circumstances, there is a conformational rearrangement of the SJ that leads to the loss of cell-cell communication. SJs are involved in the filament resealing upon RCD due to environmental stress or predation (Kieninger and Maldener, 2021).

Different structures involved in cell-cell symplastic communication evolved independently during the evolution of multicellular photosynthetic organisms, allowing intercellular molecule trafficking, signaling and differentiation (Brunkard and Zambryski, 2017; Chaigne and Brunet, 2022). Some elements are conserved across major taxonomic groups; therefore, a convergent mechanism involving intercellular symplastic movement of a death / life signal molecule would be plausible.

The potential role of extracellular vesicles in mediating cell death in photosynthetic organisms

Extracellular vesicles (EVs) are produced by organisms from all kingdoms (Kim *et al.*, 2015; Gill *et al.*, 2019). They carry a wide repertoire of molecules, e.g., proteins, lipids, different types of RNA, and serve diverse functions in disease, stress response, cell wall metabolism, systemic signaling, and both intra and interspecific communication (Schatz and Vardi, 2018; de la Canal and Pinedo, 2018; Cai *et al.*, 2019, 2021; Cui *et al.*, 2020).

Mammalian EVs have been widely studied in a medical context for their emerging roles as circulating biomarkers in degenerative diseases (Bernardi and Balbi, 2020; Teng and Fussenegger, 2021). These EVs vary in size from 50 nm to 1 µm, and can be secreted as exosomes through the endosomal pathway, as microvesicles budding from the plasma membrane, or as apoptotic bodies (Meldolesi, 2018). Interestingly, specific markers identified distinct human EVs (hEVs) that mediate different modes of cell death (Li *et al.*, 2021). For instance, hEVs related to apoptotic cancer cells are decorated by the death-receptor family member TRAIL-R2 (Setroikromo et al., 2020), whereas hEV released from Synovial fluid of Rheumatoid arthritis contain the Death-Receptor PD-1 and miRNAs that favroe PD-1 expression (Greisen et al., 2017). An abundant number of EVs are released from THP-1 monocytes undergoing lytic cell death (Baxter *et al.*, 2019).

The current knowledge on Plant EVs (plEVs) is lagging far behind compared to mammalian EVs (Rutter and Innes, 2020; Pinedo *et al.*, 2021), but emerging information on their biogenesis, composition and specific functions suggest their potential role in plant RCD-related pathways (Cui *et al.*, 2020; He *et al.*, 2021). EVs isolated from different plant sources contain similar cargos, and even overlapping proteomes related to multiple functions, i.e., hydrolytic activities, transport of ions, RNA silencing, protein and lipid signaling (Rutter and Innes, 2017; De Palma *et al.*, 2020; Pinedo *et al.*, 2021). PlEVs have been predominantly studied in the context of defense responses, which evoke changes in either plEVs composition or abundance in the extracellular space. Steady state plEVs populations increase in the apoplast of Arabidopsis leaves upon bacterial infection and in response to wounding, as well as upon SA and JA treatment (Liu *et al.*, 2020*b*). plEVs released in response to wounding-induced JA accumulation are enriched in lipids presumably precursors of JA (Liu *et al.*, 2020*a*). It remains unclear whether plEVs composition varies in response to specific stimuli, or whether the extracellular space harbors heterogeneous plEVs with different cargo. The identification of specific plEV markers is needed to explore this question. The plEV-located membrane protein tetraspanin 8 (TET8) is emerging as a potential plEV marker (Pinedo *et al.*, 2021), based on its structural similarity to the mammalian tetraspanin CD63, a diagnostic marker of a sub-type of hEVs (Jimenez-Jimenez *et al.*, 2019; Cashikar and Hanson, 2019). Arabidopsis *tet8* plants release less plEVs than wild type plants exposed to wounding (Liu *et al.*, 2020*a*).

Proteomic analysis of Arabidopsis EVs revealed the presence of a member of the plasmodesmata related remorin family, recently linked to RCD (Rutter and Innes, 2017). PlEVs might be stably incorporated by pathogenic fungi, and trigger multiple reactions such as epigenetic regulation of virulence genes, inhibition of fungal growth, and induction of RCD (Regente *et al.*, 2017; Cai *et al.*, 2018; Baldrich *et al.*, 2019). Proteomes of plEVs purified from *N. benthamiana* and Arabidopsis infected with the Turnip mosaic virus (TuMV) identified viral proteins together with plant immune response proteins (Movahed *et al.*, 2019). Viral components from TuMV that entered the host cells might be packaged into plEVs and then released into the extracellular space of the infected leaves as

a propagation strategy. Alternatively, plEVs could represent in this case a plant defense strategy, removing viral particles from the cytoplasm to prevent their spread through plasmodesmata. In this regard, isolated plEVs from Arabidopsis leaves exposed to RNAase and Trypsin activities reveal that plEV-associated RNAs are not encapsulated, but locate to the outside of plEVs, which may mediate host-induced gene silencing (Karimi et al., 2022).

A robust core of evidence shows that plEVs originate from intraluminal vesicles of late endosomes (called Multivesicular Bodies) and from the Exocyst-Positive Organelle (EXPO), and are secreted out of the cell upon fusion to the plasma membrane (Wang *et al.*, 2010; Cui *et al.*, 2020). PlEVs might also arise from the disintegration of the tonoplast in cells undergoing "*Destructive vacuolar cell death*" a HR-related fast RCD triggered by the collapse of the vacuole and the concomitant release of hydrolytic enzymes into the cytosol (Hatsugai *et al.*, 2006; Hara-Nishimura and Hatsugai, 2011, page). Under this scenario, it is plausible that plEVs enriched in vacuolar proteases would be secreted into the apoplast, and cooperate fighting pathogens present at the site of HR.

Other extracellular vesicles named paramural bodies accumulate between the plasma membrane and the cell wall in areas undergoing RCD, such as abscission zones (Bar-Dror *et al.*, 2011, page). It is conceivable that Paramural Bodies represent another type of vesicle released from the plasma membrane as part of signaling or executing mechanisms underlying RCD in certain developmental processes.

PlEVs seem to serve as stable compartments for the safe extracellular transport of different cargo. They might even be considered a functional compartment inside the extracellular compartment. Proteomic studies revealed that half of the proteins located in the apoplast of a mature leaf lack a secretion signal in their sequence and follow unconventional secretion pathways (Robinson *et al.*, 2016; Rabouille, 2017; Borniego *et al.*, 2020). PlEVs might function as a secretory pathway for these proteins (Regente *et al.*, 2012; de la Canal and Pinedo, 2018; Cui *et al.*, 2020). If plEVs represent different sub-types of vesicles with unique functions, it is conceivable that specific plEVs would be

involved in the propagation of death signals and /or death receptors, as hEVs, enhancing other, symplastic and apoplastic, death or survival mechanisms.

Vesicles are abundant in aquatic environments, but the understanding of their functions is still very limited. However, emerging information highlights the importance of EVs in cell-cell communication in aquatic microbial ecosystems and suggests a potential role in modulating cell fate. In this sense, recent studies suggest that EVs released by phytoplankton mediate a wide variety of biological functions such as energy and nutrient transfer and regulating host–virus dynamics (Biller *et al.*, 2014; Schatz *et al.*, 2017, 2021). EVs mediate viral infection in marine bloom forming *E. huxley*. In this case, EVs released by infected cells were shown to have a pro-viral function since they expedite viral infection and prolong the half-life of viruses in the environment (Schatz *et al.*, 2017, 2021), On the other hand, EVs produced by marine *Prochlorococcus* (Cyanobacteria) may prevent phage attack by acting as decoys. EVs enriched in outer membrane components would harbor phage receptors that could directly bind viral particles and thus reduce the effective titer of phages in the environment (Biller *et al.*, 2014).

Interestingly, a recent work in *Prochlorococcus* combining omic approaches (lipidomics, proteomics, and metabolomics) suggests a role of EVs in mitigating ROS toxicity. The analysis of EVs content revealed the presence of plastoquinone, oxidized carotenoid products and oxidized intact polar lipids, suggesting that vesicles might be involved in removing damaged compounds and ROS (Biller *et al.*, 2020).

The study of EVs in photosynthetic organisms is therefore key for understanding the flow of energy and information in vascular plants and aquatic environments. However, whether EVs participate in RCD in photosynthetic organisms still needs to be tested. Despite being largely overlooked so far, EVs start to be taken into consideration. The development of technologies and the use of combined approaches that allow their isolation, enumeration and molecular characterization offers a promising venue for their study in the context of cell death.

Conclusion

RCD participates in normal physiology and in stress responses in photosynthetic organisms. However, death at the cell population level is not yet well understood. Here we have reviewed the molecules that are involved in cell-cell and systemic signaling in photosynthetic organisms and their potential role in determining cell fate in neighboring cells. The examples discussed here highlight the variety of survival and death signals photosynthetic organisms across the taxonomic spectrum from phytoplankton to vascular plants, utilized to control RCD propagation during development and stress adaptation.

Ca^{2+}, ROS, lipid derivates, NO and eATP seem to play dual roles in photosynthetic organisms- death vs survival - depending on the concentration and the source, among other possible factors. However, survival or death assignment for Ca^{2+} and ROS is in some cases challenging. Considering the extracellular role of Ca^{2+} and ROS in RCD in metazoans and plants, it would be interesting to further investigate their potential function in mediating cell-cell communication during RCD in phytoplankton and macroalgae.

The development of novel approaches and techniques to investigate localized RCD responses (e.g microscopy and mass spectrometry) will be important in future studies to identify novel survival and death signals and evaluate spatiotemporal patterns of RCD. In addition, the investment on field studies is extremely important to accelerate the discovery and characterization of death and survival molecules in phytoplankton and macroalgae, and their participation in algal bloom succession.

Understanding survival and death mechanisms will reveal how different types of RCD balance communication during cell death, and is therefore an important area of research in photosynthetic organisms.

Box 1: Nomenclature of cell death used in this work

In metazoans, cell death is divided into two main types: accidental cell death (ACD) and regulated cell death (RCD). ACD is an unpreventable and uncontrollable process caused by extreme physical, chemical or mechanical triggers. In contrast, RCD involves precise signaling cascades, relies on the intracellular molecular machinery, and can therefore be modulated pharmacologically or genetically. Programmed cell death (PCD) occurs in strictly physiological scenarios (for instance, development) and represents a specific type of RCD (Galluzzi *et al.*, 2015).

In plants, cell death involved in vegetative and reproductive development is commonly referred to as developmental PCD (dPCD), while environmental PCD (ePCD) refers to cell death induced by external environmental stresses (Daneva *et al.*, 2016; Huysmans *et al.*, 2017). In phytoplankton, the term most frequently used for controlled cell death is PCD. However, the use of RCD as a term to encompass all instances of genetically encoded and actively controlled cell death has been recently proposed for plants, cyanobacteria and yeast (Carmona-Gutierrez *et al.*, 2018; Aguilera *et al.*, 2021; Distéfano *et al.*, 2021). Accordingly, in this review we will use the term to RCD in an attempt to standardize the nomenclature related to cell death in photosynthetic organisms in a precise and consistent manner.

BOX 2: Systemic signaling networks in plants

Plants possess several mechanisms that allow them to cope with different abiotic and biotic stress conditions. In addition, plant cells can activate systemic response that primethe whole plant to prepare for future challenges. These systemic responses can be divided into three major classes: (i) systemic acquired resistance (SAR), typically triggered by pathogens; (ii) systemic acquired acclimation (SAA) induced by abiotic stress, such as high light, temperature and osmotic stress; and (iii) systemic wound response (SWR) that occurs in plants upon wounding (Gilroy *et al.*, 2016; Choi *et al.*, 2017; Zandalinas *et al.*, 2020). A number of different signaling molecules, including hormones, peptides, nucleotides, RNAs and different metabolites, and mechanisms including ROS waves, the Ca^{+2} wave, electric signals, and hydraulic waves are implicated in these systemic responses (Fig. 3). (Chivasa *et al.*, 2005; Miller *et al.*, 2009; Choi *et al.*, 2014; Gilroy *et al.*, 2016; Toyota *et al.*, 2018; Choudhury *et al.*, 2018; Vega-Muñoz *et al.*, 2020, page; Fichman and Mittler, 2021). For a complete model for the propagation of rapid systemic signals during SAA and SAR see (Gilroy *et al.*, 2016).

RCD takes place as part of SAR response mechanism, for instance during the HR (Pontier *et al.*, 1998; Loebenstein, 2009), and systemic RCD (Li *et al.*, 2018). Recent studies show that local tobacco mosaic virus (TMV) infection of tomato leaves can induce systemic RCD in the root tip (Li *et al.*, 2018). Such an observation might be the result of an excessive systemic response, resulting in the death of unwanted tissue. To understand whether this RCD is a controlled, adaptive response it is necessary to evaluate the survival rate of tomato plants that show TMV-induced RCD in the root tip. Finally, during the SWR, the death of a few cells adjacent to the damaged cells results in physical closure of the wound and prevents water loss or pathogen attack (Cui *et al.*, 2013; Zandalinas *et al.*, 2020)**.**

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The authors declare no conflict of interest.

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Figure legends

Figure 1: **Simplified scheme of groups of photosynthetic organism described in this review.** Figure was inspired from Bidle 2016, Handrich, et al 2017, Cheng et al 2019 and Sánchez-Baracaldo P. 2015**.**

Photosynthetic organisms named in this manuscript,

- Cyanobacteria; *Microcystis, Anabaena sp. PCC 7120 Synechocystis sp. PCC 6803, Spirulina platensis, Prochlorococcus, Lyngbya majuscula, Trichodesmium erythraeum*
- Rhodophyta*; Mazzaella laminarioides, Glacilaria conferta, Euchema platycladum*
- Chlorophyta*; Dunalliela salina. Chlamydomonas reinhardtii. Volvox carteri, Dasycladus vermicularis* and *Acetabularia acetabulum, Ostreococcus tauri , Chlorella vulgaris, Scenedesmus obliquus,*
- Diatoms*; Skeletonema marinoi ,Thalassiosira weissflogii, Thalassiosira pseudonana* and *Phaeodactylum tricornutum*
- Raphidophytes; *Chattonella antiqua, Heterosigma akashiwo, Chattonella marina*
- Dinoflagellates, *Alexandrium minutum. Alexandrium fundyense, Alexandrium tomarense, Peridinium, Karenia bravis.*
- Phaeophytes; *Laminaria japónica, Saccarina japónica, Margalefidinium polykrikoides*
- Haptophytes; *Emiliania huxleyi*
- Bryophytes; *Physcomitrium patens*
- Vascular plants; Arabidopsis, *Phaseolus vulgaris (bean), Populus eupharatica* (poplar) , *Medicago truncatula , Nicotiana tabacum* (tobacco*), Triticum aestivum* (wheat), *Solanum lycopersicum* (tomato), *Alyssum inflatum, Euchema platycladum*

Another non-photosynthetic organisms named in this manuscript ,

Fusarium verticilloides, Pseudomonas syringae DC3000, Meloidogyne javanica, Phaeobacter inhibens, Halobacterium salinarum, Botrytis, Bacillus subtilis

Figure 2: **Examples of cell-cell communication during cell death in phytoplankton and vascular plants.**

A: Upon exposure to Cadmium (Cd^{2+} stress), Copper (Cu^{2+} stress) or salicylic acid (SA treatment), Arabidopsis cells undergo cell death and release eATP. For Cu stress and SA treatment, eATP acts as a survival signal for surrounding cells (cells in green), whereas during Cd^{2+} stress eATP induces cell death (yellow cells), thereby acting as a death signal.

B: *Phaeodactylum tricornutum* exposed to grazing undergoes cell lysis and releases the oxylipin (2E,4E/Z)-decadienal (DD). Exposure to high (lethal) concentrations of DD leads to cell death in surrounding cells, whereas low (sub-lethal) concentrations lead to acclimatation and further resistance to lethal concentrations of DD.

Dark orange arrows represent regulated cell death induction, whereas pink arrows represent release of survival/death signals

Figure 3: **Systemic signalling in plants.** Hypersensitive response, wounding and tobacco mosaic virus (TMV) infection generate ROS, hydraulic signals and Ca^{2+} waves, among other signals.The individual signals are proposed to interact and are transmitted long-distance, sometimes across the whole plant. TMV infection in leaves induces also systemic PCD in roots.

Table 1. Cellular signaling molecules with pivotal functions in stress surveillance and cell death induction and propagation in photosynthetic Organism

Molecule	Signal classification	Organism	Species	Treatment	Results	Reference
Extracellular ATP	Death	Vascular plant	*Phaseolus vulgaris* leaves *Nicotiana tabacum* leaves	Non-hydrolyzable ATP analog.	Macroscopic RCD Systemic RCD in tobacco	Chivasa et al., 2005
			Populus euphratica cell suspension	Exogenous ATP	Ca and ROS production Cytochrome c release from mitochondria Activation of caspase-like proteases DNA fragmentation	Sun et al., 2012
			Arabidopsis leaves	Cadmiun stress	Cd stress induces eATP release ATP secretion correlates with electrolyte leakage	Hou et al., 2017
	Survival		Arabidopsis cell culture Arabidopsis leaves	eATP depletion	Dose-dependent reduction in cell viability	Chivasa et al., 2005
			Nicotiana tabacum cell suspension	Salicylic acid	RCD induction RCD is alleviated by exogenous ATP eATP-mediated increased cell viability is mediated by Ca uptake	Feng et al., 2015 a, b
			Nicotiana tabacum cell suspension Wheat root seedlings	Copper stress	ATP is secreted upon copper-induced cell death eATP released by dying cells alleviates cell death in neighbouring cells	Jia et al., 2019
			Arabidopsis seedlings	Fungal toxin (FB1)	FB1-induced RCD reduces eATP levels Exogenous ATP prevents FB1-induced RCD FB1-induced systemic RCD is suppressed by eATP	Smith et al., 2021
Peptides	Death	Vascular plant	Arabidopsis cell culture Arabidopsis leaves	Bia	Participates in xylem differentiation Enhances wounding-induced RCD	Escamez et at., 2019

			Arabidopsis leaves	Gri	Involved in extracelular ROS-induced RCD Induces superoxide-dependent RCD	Wrzaczek et al., 2009 Wrzaczek et al., 2015
			Arabidopsis roots	PEP1	Participates in wounding/damage response Perceived in neighbouring by PEPR1 and BAK1 PEP1 perception induces RCD	Hander et al., 2019
			Arabidopsis leaves	KOD	Suspensor cell RCD Infiltration induces RCD and mitochondrial disfunction RCD depends on caspase-like activity Expression induced by biotic and abiotic stress	Blanvillain et al., 2011
	Survival	Vascular plant	Arabidopsis cell culture Arabidopsis leaves	Kratos	Participates in xylem differentiation Limits ectopic RCD during xylem differentiation and wounding	Escamez et at., 2019
		Cyanobacteria	*Microcystis aeuroginosa*	Microcystin	Promotion and maintenance of colonies	Hu and Rzymski 2019 Gan et al., 2012
Extracellular Ca^{2+}	Death	Vascular plant	Tomato leaves	Tobacco Mosaic Virus (TMV)	Infection on leaves induces Ca2+ and ROS signalling in root tips. RCD at 20dpi in root tips	Li et al., 2018
			Arabidopsis roots	Heat shock-induced RCD	RCD is inhibited by the extracellular Ca2+ chelator EGTA	Distéfano et al., 2017
			Arabidopsis cell culture	Exposure to ceramides	LaCl3 inhibits ceramide-induced RCD RCD is independent of the generation of ROS.	Townley et al., 2005
			Alyssum inflatum cell suspension culture	Exogenous Ca+2	RCD induction High levels of ROS and lipid ROS	Ghasemi et al., 2020
			Rice root tips	Salt stress	LaCl3 prevents salts-stress induced LaCl3 inhibits ROS production	Li et al., 2007

	Death/Survival	Vascular plant	Arabidopsis leaves	Wounding	Long-distance transmission of Ca2+ through PD and phloem Systemic defense response	Toyota et al., 2018
	Survival	Cyanobacteria	*Synechocystis* sp. PCC 6803	Heat shock-induced RCD	Inhibition of heat shock-induced RCD	Aguilera et al., 2022
ROS	Death	Vascular plant	Arabidopsis leaves	Avirulent PstDC3000	ROS burst and RCD reduced in *rbohd* and *rbhof* mutants	Torres et al., 2002
		Red algae	*Glacilaria conferta*	Cell wall fragments	ROS burst (*)	Weinberger *et al.*, 2005
			Euchema platycladum	Wounding	ROS burst (*)	Collen & Pedersen, 1994
		Diatoms, dinoflagellates, chlorophytes and haptophytes	*Thalassiosira pseudonana,* *Karenia bravis, Emiliania huxleyi* (…)	Abiotic stress or infection by viruses	ROS burst inducing RCD	Bidle, 2015
	Survival	Vascular plant	Arabidopsis leaves	Superoxide and salicylic acid	Runaway RCD in *lsd1/rbhod* and *lsd1/rbohf* mutants	Torres et al., 2005
		Raphidophytes and dinoflagellates	*Chattonella antiqua, Heterosigma akashiwo, Margalefidinium polykrikoides*	Growth in batch cultures	Positive relationship between production of eROS and growth rate	Diaz and Plummer 2018
		Cyanobacteria and Raphidophytes	*Lyngbya majuscula*, *Trichodesmium erythraeum* and *Chattonella marina*	Iron acquisition	Growth facilitation *via* an increase in iron bioavailability due to eROS production	Diaz and Plummer 2018

		Dinoflagellates	*Alexandrium tamarense*	Abiotic stress	Intracellular ROS accumulation inducing quiescence through encystment	Jauzein and Erdner 2013
Oxidized lipids/ lipid-derived molecules	Death	Vascular plant	Arabidopsis protoplasts	Jasmonic acid derivatives	ROS burst Mitochondria and chloroplast dysfunction Dose-dependent RCD	Zhang & Xing, 2008
		Diatom	*Thalassiosira weissflogii*	Decadienal-like aldehydes	NO production Transient increase in cytosolic Ca2+ RCD induction	Vardi et al., 2006
			Phaeodactylum tricornutum	Decadienal-like aldehydes	Increased intracellular ROS and NO RCD induction	Vardi et al., 2006
			Skeletonema marinoi	Sterol sulfates	RCD induction	Gallo et al., 2017
		Green algae	*Emiliania huxleyi*	Viral glycosphingolipids	RCD induction RCD depends on ROS, NO and caspase-like activity	Vardi et al., 2009, 2012)
	Survival	Diatom	*Phaeodactylum tricornutum*	Decadienal-like aldehydes	Sublethal doses promote resistance to lethal concentrations	Vardi et al., 2006
Extracellular NO	Death	Vascular plant	*Nicotiana tabacum* cell suspension	Hypersensitive response	NO and ROS induce RCD	Laxalt et al. 2007
		Diatom	*Thalassiosira weissflogii* *Phaeodactylum tricornutum*	Abiotic stress	RCD in a dose dependent manner	van Creveld et al., 2015; Vardi et al., 2006 Vardi , 2008
	Survival	Vascular plant	Barley embryo	Gibberellin	Non-enzymatic production of extracellular NO by aleurone ROS-dependent RCD of aleurone cell layer NO donors delay RCD	Bethke et al., 2001; 2004

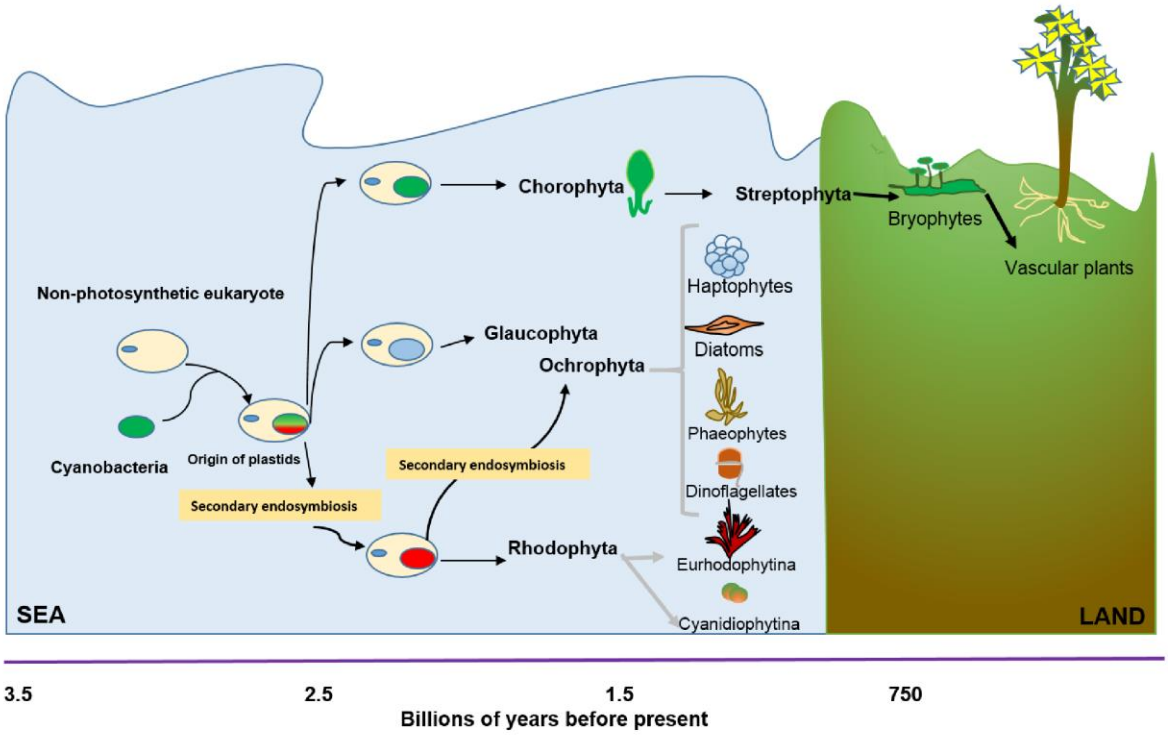

Figure 1: **Simplified scheme of groups of photosynthetic organism described in this review.** Figure was inspired from Bidle 2016, Handrich, et al 2017, Cheng et al 2019 and Sánchez-Baracaldo P. 2015 **.**

Photosynthetic organisms named in this manuscript ,

- Cyanobacteria; *Microcystis, Anabaena sp. PCC 7120 Synechocystis sp. PCC 6803, Spirulina platensis, Prochlorococcus, Lyngbya majuscula, Trichodesmium erythraeum*
- Rhodophyta*; Mazzaella laminarioides, Glacilaria conferta, Euchema platycladum*
- Chlorophyta*; Dunalliela salina. Chlamydomonas reinhardtii. Volvox carteri, Dasycladus vermicularis* and *Acetabularia acetabulum, Ostreococcus tauri* , *Chlorella vulgaris, Scenedesmus obliquus,*
- Diatoms*; Skeletonema marinoi ,Thalassiosira weissflogii, Thalassiosira pseudonana* and *Phaeodactylum tricornutum*
- Raphidophytes; *Chattonella antiqua, Heterosigma akashiwo, Chattonella marina*
- Dinoflagellates, *Alexandrium minutum. Alexandrium fundyense, Alexandrium tomarense, Peridinium, Karenia bravis.*
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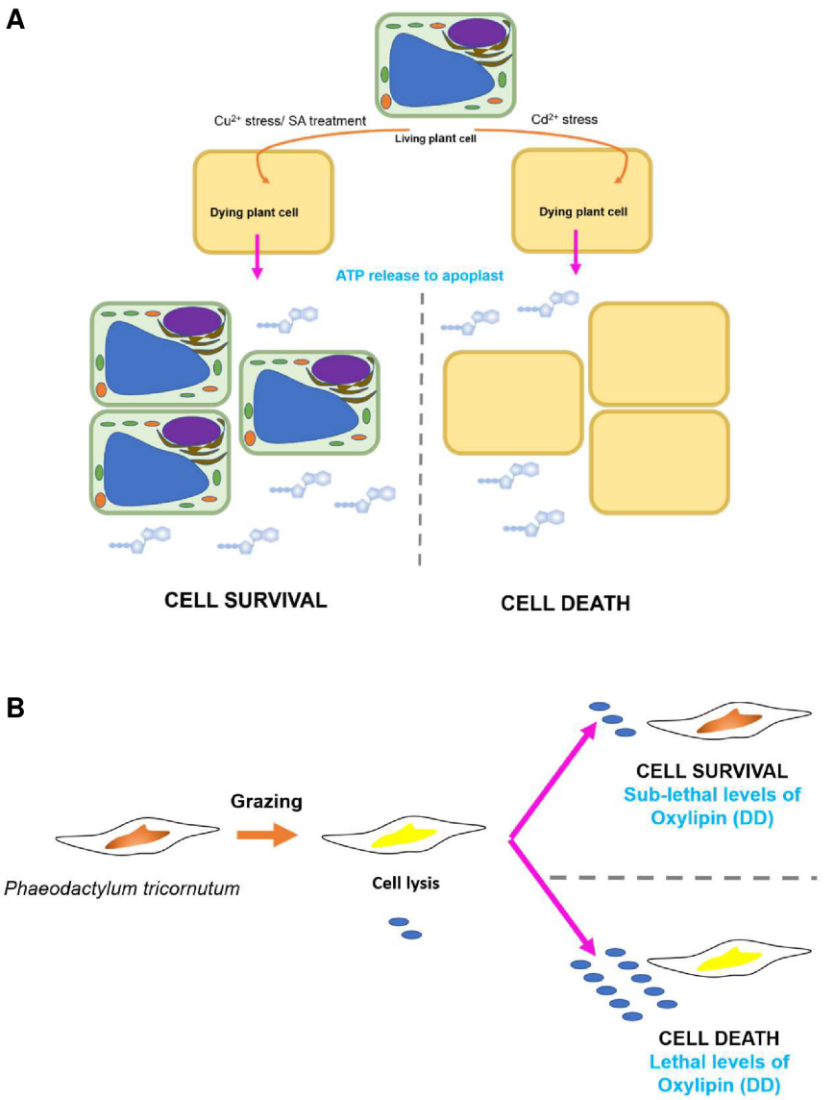

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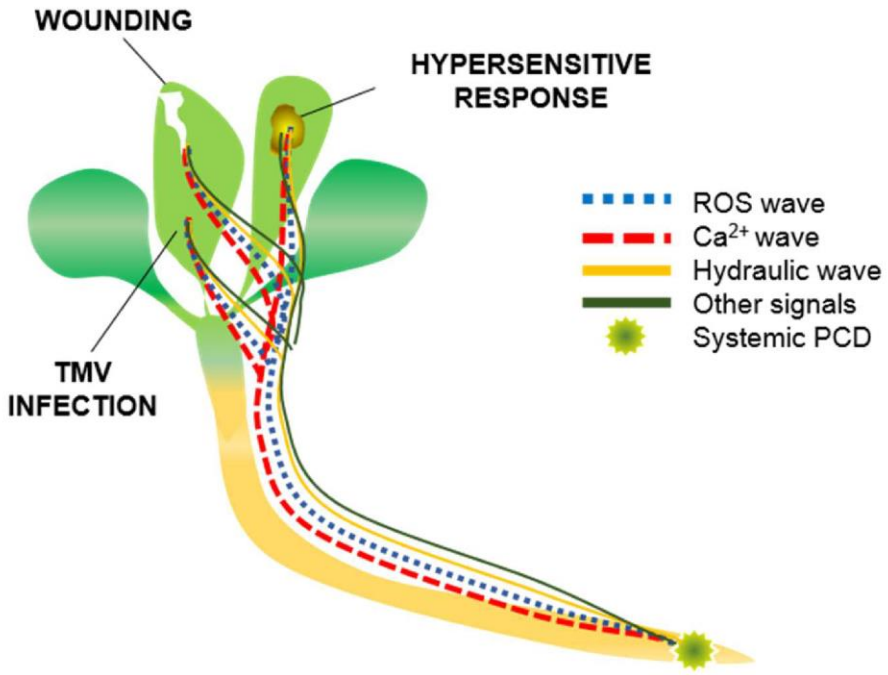

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