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WHAT IS MISSING TO CREATE NEW HERBICIDES AND SOLVING THE PROBLEM OF RESISTANCE?

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The issue of weeds resistance to herbicides and potential solutions of this problem are considered. Alternatives to chemical methods of weed control are discussed. It is concluded that the introduction of alternative methods of weed control will reduce the relative part of herbicides in crop protection technologies, but complete rejection of the use of herbicides is unlikely. At the same time, the problem of resistance requires significant improvement of the chemical method, primarily by reducing the directed selection pressure of herbicides. It is stated that the most effective way to managing resistance is the complex application of herbicides with different mode of action. The requirements for anti-resistant herbicide compositions are discussed. It is noted that the current range of herbicides limits the choice of components for creating such compositions. It is concluded that the development of new effective herbicides with mode of action distinct from existing ones is necessary to managing resistance. Methods for finding new sites of herbicide action and causes for the unsatisfactory effectiveness of their implementation are discussed. The opinion is substantiated that to determine the criteria for choosing new sites of herbicide action, it is necessary to elucidate the mechanisms of herbicide-induced pathogenesis, and data on the involvement of programmed cell death in this process are discussed. Another important direction of research, necessary for determining these criteria, is the study of feedback loops that regulate the functioning of metabolic pathways and physiological systems of plants. The data on the peculiarities of the functioning of feedback loops, which control the expression of genes encoding the sites of action of the most effective classes of herbicides, are discussed.

Key words: herbicides, resistance, new sites of action, herbicide-induced pathogenesis, programmed cell death, feedback regulation.

Weed control is a necessary condition for realizing the genetic potential of agricultural crops productivity. Since the discovery of the phenomenon of selective phytotoxicity and the development of the first selective herbicides in the middle of the last century, the chemical method of weed control has been constantly improving, and gradually took the dominant place in crop protection technologies [1, 2]. However, the widespread use of herbicides has caused the strong selection pressure leading to the emergence of weeds herbicide-resistant biotypes [2—8]. Resistance to most classes of modern

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herbicides has been recorded in hundreds of weed species in many countries around the world [9]. The most widespread resistant biotypes have emerged in countries with high levels of industrial development, particularly in the USA [9]. In Ukraine, three cases of herbicide resistance have been registered to date [10].

Two types of resistance are distinguished: «target site resistance» (TSR) which confers resistance to herbicides with a specific mode of action, and «non-target site resistance» (NTSR) which can confer resistance to herbicides from different classes. TSR is primarily caused by mutations in genes encoding herbicide target proteins [4, 5, 7, 8]. Increasing the amount of target protein through increased gene expression or duplication (amplification) is an important but less common mechanism of TSR [8]. NTSR can be caused by reduced absorption or translocation, increased metabolic degradation of herbicides [11—13], or enhanced resistance to herbicide-induced stress [14—17]. The genetic mechanisms responsible for NTSR are more complex than for TSR [7, 18]. These mechanisms may include genes that are members of large gene families, including genes encoding enzymes involved in herbicide degradation [11, 12, 19]. It is evident that cross-resistant biotypes, resistant to different herbicides [20—23], and multi-resistant weed biotypes, whose resistance to different herbicides is caused by more than one mechanism [22, 24, 25], are particularly dangerous. The spread of herbicide resistance among weeds reduces the effectiveness of crop protection and in general casts doubt on the prospects of further using the chemical method of weed control. Therefore, there is an active discussion about the fundamental possibility and specific ways to address the issue of resistance [26—28].

The spread of herbicide resistance prompts the search for alternative to chemical methods of weed control [29—31]. This includes the development of biological methods using plant pathogens [31], enhancing the competitiveness of crops through the use of their allelopathic activity [31—34], improving agronomic practices [35], and the adoption of advanced physical weed control methods, including robotics [31, 36, 37]. However, none of these alternative methods currently can compete with synthetic herbicides. Microbial bioherbicides, for instance, have not gained widespread use due to issues related to their narrow spectrum of activity, high dependence on environmental conditions, and persistence [38]. Therefore, while the relative part of herbicide use in integrated crop protection technologies may be reduced through the broader adoption of alternative weed control methods [39], complete abandonment of herbicide use in the near future is unlikely [31]

Since the development of resistance is a consequence of the selection pressure exerted by herbicides, managing resistance requires reducing the directedness of this pressure [40—42]. In this regard, the role of crop rotation is obvious, since herbicides with different mode of action can be easily rotated during crop rotation. However, the trend towards specialized and shortened crop rotations limits the opportunities for herbicide rotation. Additionally, there is a clear desire to use the most effective and environmentally safe herbicides, in particular ALS inhibitors, for crop protection. On the one hand, the creation of non-GMO hybrids of rapeseed [43—45], soybean [46—48] and sunflower [44, 49, 50], resistant to ALS inhibitor

herbicides, significantly increases the effectiveness of these crops protection. On the other hand, it leads to the continuous use of ALS inhibitor herbicides throughout the crop rotation, which, in turn, promotes the development of resistance to these herbicides. Therefore, the most effective means of preventing resistance and controlling existing resistant biotypes is the complex application of herbicides with different mode of action for the protection of individual crops [42, 51, 52]. In certain cases, a synergistic combination of several herbicides with the same mode of action may prove effective for controlling resistant weed biotypes [53, 54]. Nevertheless, the effectiveness of combating resistance increases with the use of a greater number of herbicides with different mode of action in the combination [55].

In this regard, the introduction of transgenic crops resistant not to one, but to several different herbicides is being implemented [56—59]. Compositions of selective herbicides should be used to manage resistance in common crops. Although these compositions are composed of herbicides with different mode of action, the action spectrum of the components should be as close as possible [42]. This characteristic fundamentally distinguishes anti-resistance compositions from traditional ones, in which components were selected to complement each other in terms of action spectrum [60]. Therefore, each components of anti-resistance compositions must have the widest possible action spectrum to ensure high protection efficiency. The interaction of components, which must be either synergistic or at least additive, is of particular importance for anti-resistance compositions [41]. This also differentiates anti-resistance compositions from traditional ones, in which antagonistic reduction of phytotoxicity of one of the components was allowed, if it was directed at crop plants [60]. As a result, an important requirement is the high selectivity of the components of anti-resistance compositions towards crop plants, so that the synergistic or additive nature of their interaction does not lead to damage to crop plants. Satisfying these requirements, especially regarding the nature of the interaction, is quite difficult, since antagonism is much more common phenomenon than synergism[61].

Synergistic interaction is observed when herbicides from the class of synthetic auxins are combined with ALS inhibitors [62]. Therefore, compositions of ALS inhibitors with synthetic auxins 2,4-D and dicamba, which are widely used for the protection of cereal crops and maize, can be considered as a means to manage resistance. However, while in some countries of Central and Eastern Europe, such compositions can be used to protect winter wheat crops both in spring and autumn [63], under the conditions of Ukraine, the application of 2,4-D and dicamba in autumn is practically impossible. Due to this, complex herbicide preparations containing ALS inhibitors and the carotenoid synthesis inhibitor diflufenican, whose site of action is phytoene desaturase, are used in Ukraine for autumn application in winter wheat crops.

Since resistance to ALS inhibitors is the most widespread, a search for alternative options for complex herbicide application was conducted. Herbicides from the classes of electron transport (ET) and protoporphyrinogen oxidase (PPO) inhibitors are characterized by a wide spectrum of action in addition to inhibitors of carotenoid synthesis. The effects of

interaction were studied in binary and triple mixtures of diflufenican, the ET inhibitor metribuzin, and the PPO inhibitor carfentrazone. It was established that in mixtures of diflufenican with metribuzin and carfentrazone the interaction is additive, while in the case of metribuzin with carfentrazone, it is antagonistic. When diflufenican is added to metribuzin and carfentrazone, the character of the interaction changes from antagonistic to additive [64]. In terms of weed control effectiveness, the mixture of diflufenican with metribuzin, and the triple mixture with the addition of carfentrazone were not inferior to the action of the composition of diflufenican with ALS inhibitors florasulam and penoxsulam [65]. Considering the different mode of action, as well as the width and intersection of the action spectra, it can be concluded that the mixture of diflufenican with metribuzin and the triple mixture of diflufenican, metribuzin, and carfentrazone can be means for managing resistance [65].

For the protection of sunflower crops, complex formulations or tank mixtures are used, which include inhibitors of the very long-chain fatty acids (VLCFA) synthesis, and ET inhibitors. A typical representative of such compositions is the complex herbicidal formulation Primextra TZ Gold, the active ingredients of which are the VLCFA inhibitor S-metolachlor and the ET inhibitor terbuthylazine. Since the components of such compositions complement each other in terms of action spectrum, and the intersection of these spectra is only partial, such compositions cannot be considered completely anti-resistant. Therefore, the effects of interaction and the effectiveness of weed control were investigated on sunflower crops with the combined use of the carotenoid synthesis inhibitor aclonifen and the ET inhibitor prometrin, the spectrum of which is similar. It was shown that the interaction of aclonifen with prometrin is additive. In terms of weed control effectiveness, the mixture of aclonifen with prometrin was not inferior to the action of the herbicide Primextra TZ Gold [66]. Thus, it can be considered that the application of tank mixtures of herbicides aclonifen with prometrin in sunflower crops may be a factor managing resistance.

For the protection of maize crops, complex formulations and tank mixtures are used, which consist of herbicides ALS inhibitors, and inhibitors of carotenoid synthesis, which site of action is hydroxyphenylpyruvate dioxygenase (HPPD). However, such compositions are characterized by antagonistic interaction, leading to low effectiveness of some resistant weed species control [67, 68]. Due to this, such compositions cannot be considered anti-resistant. When combining HPPD inhibitors with ET inhibitors, the interaction is synergistic, which allows for effective control of a wide range of weed species, including those resistant to individual components of such compositions [68—72]. Therefore, there is every reason to consider the application of herbicidal compositions consisting of HPPD and ET inhibitors in maize crops as an effective means of combating resistance.

Thus, the existing range of herbicide active substances allows for the creation of anti-resistant compositions for the protection of main agricultural crops. However, it should be noted that the necessity to ensure conditions of anti-resistance, forces to make certain compromises. Thus, the replacement of ALS inhibitors with ET inhibitors in compositions for the protection of maize crops and autumn application in winter wheat crops

leads to a significant increase in pesticide pressure on agrophytocenoses, since the effective dose of ET inhibitor herbicides exceeds ALS inhibitors by two orders of magnitude. Permanent use of ET inhibitors in anti-resistant compositions is also not optimal, as the prevalence of resistance to ET inhibitors inferior only to the prevalence of resistance to ALS inhibitors.

Therefore, there is a general consensus that to overcome resistance, it is necessary to expand the range of herbicides by creating new highly effective active substances with mode of action distinct from existing ones [73—76]. It is emphasized that herbicide combinations with different mode of action allow to control biotypes with TSR but do not solve the problem of NTSR, which requires the development of fundamentally new herbicides capable of inhibiting xenobiotic detoxification systems. However, over the past three decades, the range of herbicides has not expanded, but rather has diminished [2]. This is due, on the one hand, to the increase in ecotoxicological requirements for pesticides, resulting in the removal of certain active substances and even classes of herbicides from the assortment. On the other hand, the process of creating new herbicides has stalled. While over 50 years since the discovery of selective phytotoxicity, over 200 active substances of herbicides with about 30 different modes of action have been commercialized, in the last 30 years, no herbicide with a new mode of action has been registered [2, 73, 76].

One of the factors that have slowed down the creation of new herbicides is the development of transgenic crops resistant to the non-selective herbicide glyphosate, which has reduced the market for selective herbicides and, consequently, reduced incentives for searching of new herbicides [73]. However, in our opinion, the main reason is that cost of searching for new herbicides, which until recently was carried out by the method of empirical screening, has increased significantly. One of the consequences of this increase has been the consolidation and mergers of crop protection companies [77]. However, the absence of new herbicides indicates that even for large companies, investments in the search for new herbicides are too risky.

The costliness of empirical screening has led to the application of advanced molecular-biological and genomic methods in the search for new sites of herbicide action. However, unlike pharmacology, where these methods have led to the creation of many new drugs, the discovery of new sites of herbicide action has not occurred [2, 73]. While new herbicides have indeed been created, their low effectiveness prevented them from competing with existing herbicides [78]. In this case, the failure was due to the fact that the choice of the protease CtpA as a new site of action was based on data that a mutation in the gene encoding this enzyme is lethal. However, it turned out that only a mutation causing 100 % «silencing» of the gene is lethal, while partial suppression of its expression does not significantly affect the vitality of plants. Since a very high concentration of the inhibitor was required for 100 % inhibition of enzyme activity, the effectiveness of the new herbicide accordingly turned out to be very low [78]. To avoid such a situation, «knockdown» genes can be used to select sites of herbicide action, but there is no information in the open literature about the success of such attempts [73].

Considering the existence of three classes of herbicides, the phytotoxic action of which is due to the blocking of amino acid synthesis, the pos-

sibility of searching for new sites of herbicide action among other enzymes of these metabolic pathways is discussed. It is emphasized that an effective herbicide must not only inhibit its target enzyme to ensure phytotoxicity but must also have a cascading effect on the relevant pathways critical for plant growth and development [79]. However, there are doubts about the productivity of this approach. In particular, the herbicidal activity of the phytotoxin asperphenolic acid produced by the fungus *Aspergillus terreus* is due to the inhibition of dihydroxy acid dehydratase (DHAD), the last enzyme in the branched-chain amino acid biosynthesis pathway [80]. However, the herbicidal activity of asperphenolic acid significantly lags behind the activity of existing synthetic herbicides. Therefore, it is unknown whether DHAD could be a promising site of herbicide action [74]. The same applies to the enzyme following ALS in the branched-chain amino acid biosynthesis pathway — ketol-acid reductoisomerase (KARI), as the found inhibitors of this enzyme are significantly less effective than ALS inhibitors [81]. The opinion expressed that preference for ALS as the site of action over DHAD and KARI is due to the fact that mechanism of inhibiting ALS activity by certain herbicides is accompanied by the destruction of the cofactor thiamine diphosphate [74]. This hypothesis certainly deserves attention, but it is necessary to clarify why the degradation of the cofactor is more effective from the perspective of herbicidal action than the direct inhibition of enzyme activity.

To select new sites of action, it is proposed to use information regarding the action of phytotoxins [82]. Assuming that herbicidal effect is observed at low concentrations of the phytotoxin, this approach is undoubtedly promising. Confirmation of this is the highly effective herbicides, the inhibitors of HPPD, which are synthetic analogs of the natural compound leptospermon found in certain species of *Myrtaceae* family plants [83]. However, if a natural phytotoxin acts at high concentrations, there is no guarantee that its synthetic analogs will possess high herbicidal activity.

New genomic approaches have been proposed for the discovery of new herbicide mode of action [75]. The first of the proposed approaches is based on data that concentrations of certain phytotoxic metabolites, such as protoporphyrin IX, are maintained by plants *in vivo* at very low levels, and the rapid increase in the content of this metabolite is a consequence of the action of herbicides which are the inhibitors of PPO. Therefore, to identify new sites of herbicide action, it is proposed to investigate the phytotoxicity and sizes of pools of all primary metabolites. The second approach involves determining reactions that occur at very low levels of enzyme content. It is assumed that inhibiting reactions involving a large number of enzyme molecules will require a large amount of herbicide, whereas at low enzyme levels, a small herbicide concentration will be sufficient.

In some publications, it has been noted that while the sites of herbicides of many classes action are well known, the specific mechanisms by which herbicides kill plants is unknown [84, 85]. This is especially true for herbicides whose phytotoxic effects develop slowly, and the time interval between herbicide application and plant death is quite large. In this regard, the possibilities of using genomics, transcriptomics, and metabolomics to

study the response of differentially sensitive plants to herbicide action are discussed [85]. Studies of photosynthesis, leaf proteomes, amino acid profiles, and redox profiles have been conducted in sensitive and glyphosate-resistant varieties of soybean (*Glycine max*) [84]. In leaves of the resistant variety, much more glyphosate accumulated than in leaves of the sensitive variety. At the same time, in the resistant variety, changes in amino acid metabolism were relatively insignificant. Glyphosate in the leaves of the resistant variety did not affect photosynthesis, but a decrease in the amount of photosynthesis/photosynthetic pathway proteins was observed, along with oxidation of the main redox pools. In contrast, in the sensitive variety, glyphosate treatment quickly suppressed photosynthesis and led to the appearance of a nitrogen-rich amino acid profile. In this case, there was no oxidation of the redox pools in the sensitive variety, but an increase in the content of protective proteins occurred [84].

It was shown, that in the sensitive biotype of *Amaranthus palmeri*, glyphosate treatment led to an increase in *de novo* amino acid synthesis in combination with the inhibition of protein synthesis and an increase in protein catabolism [85]. The study of the metabolomic profile of *A. palmeri* plants under the influence of glyphosate showed that plants death was not caused by the absence of aromatic amino acids, since in glyphosate-treated plants, the content of amino acids, including aromatic ones, increased [86]. Although it is obvious, that this increase is a consequence of accelerated protein catabolism caused by the inhibition of 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS) activity by glyphosate and the resulting deficit of aromatic amino acids [87]. In the resistant biotype of *A. palmeri* after glyphosate treatment, less damage by reactive oxygen species (ROS) was observed, and higher activity of antioxidant defense was observed compared to the sensitive biotype [88]. Under the influence of glyphosate, 80 % of metabolites, including shikimate, which accumulated in the sensitive biotype of *A. palmeri*, also accumulated in the resistant biotype. However, in the resistant biotype, glyphosate primarily caused the accumulation of glycosides of dihydroxylated and methoxylated flavanols with higher antioxidant potential [89].

Differential expression analysis of genes in response to glyphosate action allowed the identification of new genes that may be associated with glyphosate resistance. Among them were found genes encoding enzymes involved in herbicide transport and metabolism, as well as genes encoding enzymes of antioxidant defense [90]. Thus, it was shown that the induced metabolic changes in plants under the influence of glyphosate are not limited to the shikimate pathway, but include active reactions aimed at protecting against the herbicide [84, 88—90]. This conclusion applies not only to glyphosate. Activation of antioxidant defense systems was observed in a mutant of rapeseed (*Brassica napus*) resistant to the ALS inhibitor tribenuron-methyl in response to the action of this herbicide [91].

Thus, there are grounds to believe that the final magnitude of herbicide phytotoxic action is determined by the interaction of various processes induced by herbicide in the plant. The arguments in favor of this proposition were first obtained when studying the effects of herbicide interactions. In particular, it was established that the antagonistic reduction of the phytotoxic action of herbicides acetyl-CoA-carboxilase (ACC)

inhibitors when complexed with herbicides ALS inhibitors is not due to a decrease in the inhibitory effect on ACC activity [92]. This led to the conclusion that the phytotoxic action of herbicide is not solely determined by its interaction with the target site, but depends on the course of processes initiated by this interaction. The term «pathogenesis induced by herbicides» was proposed to describe the set of events, beginning with the herbicide's interaction with the target site and ending with the damage or death of plants [93].

It is obvious, that reactions aimed at protecting the plant from the herbicide's action are an active response to stress. This raises the question of the nature of the pathological processes that lead to plant death. Are they a passive cascade of consecutive damages, or does the process of pathogenesis induced by herbicides contain an active component? The hypothesis regarding the active nature of herbicide-induced pathogenesis finds support in the well-known fact that death of cells under the influence of various biotic and abiotic stressors occurs through an active, genetically controlled process of apoptosis, or more precisely, programmed cell death (PCD). Therefore, it is entirely valid to assume the possible involvement of PCD in herbicide-induced pathogenesis. It was shown, that the introduction of the animal anti-apoptotic gene *Bcl-2* into the tobacco chloroplasts led to increased tolerance to herbicides paraquat, acifluorfen, and sulfentrazone. While wild tobacco plants, treated with these herbicides, died with signs of apoptosis, transgenic plants survived without any apoptotic signs [94]. The introduction of the anti-apoptotic gene *p35* of baculovirus into the genome of passion fruit plants by biobalistics methods increased their tolerance to the herbicide glufosinate [95]. When treating soybean plants, which are moderately tolerant to lactofen herbicide, the appearance of necrotic spots in the contact zone was observed. This cell death was accompanied by autofluorescence, similar to what occurs at hypersensitive reactions. It was also found that induction of the homologous gene *Hsr203j* (which is a marker gene of hypersensitive response in tobacco) happened under the action of lactofen [96].

The cysteine-dependent proteases, named caspases, are the important components of animal apoptosis. Plants encode only distant homologues of caspases, the metacaspases that are involved in PCD, but do not possess caspase-specific proteolytic activity. Nevertheless, plants do display caspase-like activities indicating that enzymes structurally distinct from classical caspases may operate as caspase-like proteases. Novel PCD-related subtilisin-like protease named phytaspase (plant *asp*artate-specific prote*ase*) has been identificated. Phytaspase is constitutively secreted into the apoplast before PCD, but is re-imported into the cell during PCD. It was observed the appearance of phytaspase in the cytoplasm under oxidative stress created in plant cells by the herbicide paraquat [97].

The ability to induce PCD in plant cells was established in the study of the antimitotic activity of new herbicides of dinitroaniline derivatives when complexed with ACC inhibitor herbicides. It was shown, that treatment of plants with these compositions induced cell death in the roots of barley and radish seedlings, accompanied by cytoplasm acidification. In addition, *in situ* analysis using the TUNEL method revealed that under the action of the dinitroaniline and ACC inhibitors mixtures, DNA fragmen-

tation occurred, indicating DNA fragmentation by nucleosomes [98]. Electrophoretic study of the nature of DNA degradation in the maize roots meristems under the action of the herbicide ACC inhibitor haloxyfop-ethyl and in sunflower leaves under the action of the herbicide ALS inhibitor tribenuron-methyl showed that at the beginning chaotic DNA degradation occurs. After some time, the ladders appeared on the electrophoregrams, indicating DNA fragmentation by oligo-mononucleosomes [99, 100].

Thus, these studies showed that cell death under the action of ACC- and ALS-inhibiting herbicides has signs of both necrosis, characterized by chaotic DNA degradation, and apoptosis, characterized by DNA fragmentation into nucleosomes. This conclusion does not contradict the hypothesis of the involvement of PCD in herbicide-induced pathogenesis. Only in the early stages of the cell death mechanisms investigation, the apoptosis, as an active energy-dependent process realized by launching a genetically programmed cascade of reactions, was opposed to the necrosis, which was considered an uncontrolled process that did not require the expenditure of the cell's own energy [101]. However, further research has shown that the appearance and course of necrosis can be tightly regulated [102, 103]. Thus, according to modern concepts, necrosis is considered one of the variants of PCD (PCD III) [104].

DNA fragmentation, detected by the TUNEL method, occurs in the cells of the root meristems of sensitive plant species under the action of herbicides ACC and ALS inhibitors. This fragmentation is associated with increased activity of endogenous nucleases, which is the evidence of the regulated and active nature of pathogenesis induced by these herbicides, and therefore the participation of PCD in this pathogenesis [105]. The increased survival of cells under the action of the herbicide ALS inhibitor tribenuron-methyl, with prior treatment with an inhibitor of animal caspases, is also evidence of the PCD participation in the pathogenesis induced by this herbicide [100].

According to modern concepts, programmed cell death (PCD) can occur through three mechanisms: apoptosis [PCD I], autophagy [PCD II], and necrosis [PCD III] [104]. It is known that ROS are universal inducers of PCD, including autophagy. Therefore, the activation of autophagy as a consequence of the herbicides action, the phytotoxic effect of which is due to the violation of photosynthesis, and mediated by the ROS formation, is quite expected. For example, activation of autophagy in *Chlamydomonas reinhardtii* cells was observed under the action of the herbicide norflurazon, which is an inhibitor of carotenoid synthesis [106]. Activation of autophagy was observed under the action of the herbicide paraquat, which acts as an electron acceptor in PS I of chloroplasts in *Nicotiana benthamiana* plants [107]. In mutant plants with suppressed autophagy, sensitivity to paraquat was significantly higher, compared to wild-type plants [108, 109], and conversely, stimulation of autophagy contributed to a reduction in the phytotoxic effect of paraquat [110].

The interaction of herbicides with autophagy is also traced in the case of herbicides that inhibit microtubule formation. Since microtubules play an important role in the functioning of autophagy [111], herbicides that are inhibitors of microtubule formation are capable of suppressing the formation of autophagosomes [107]. This may explain the synergism in the mix-

tures of ACC inhibitor herbicides with herbicides derived from dinitroaniline, which are known to be inhibitors of microtubule formation [98].

Autophagy-induced cell death was observed in pollen grains of rapeseed plants, treated with the herbicide ALS inhibitor tribenuron-methyl [112]. Significant results regarding the role of autophagy in determining plant tolerance to the action of ALS inhibitor herbicides were obtained through a comprehensive study of autophagy activation in wild-type and autophagy-deficient mutants of *Arabidopsis*, treated with the herbicide tribenuron-methyl [113]. After treatment with tribenuron-methyl, the transcript levels of almost all *ATG* genes, responsible for autophagy induction, increased in wild-type seedlings. Observation of autophagic activity in tribenuron-methyl-treated seedlings using transmission electron microscopy (TEM) revealed extensive formation of classical double-membraned autophagosomes in the cytoplasm, and autophagic bodies with a single membrane in the cell vacuoles. Quantitative assessment of autophagic activity by TEM showed, that autophagic activity in leaves increased 3.2 times after treatment with tribenuron-methyl. In addition, autophagy activation was tracked by determining the levels of the ATG8 protein and its complex with green fluorescent protein (GFP)-ATG8E. Accumulation of ATG8 was detected after 6 hours, and the maximum level of this protein was observed after 24 hours of treatment with tribenuron-methyl. Correspondingly, the free GFP protein content began to accumulate after 12 hours of treatment with tribenuron-methyl, and reached a maximum after 48 hours of treatment. All of these data indicate that the herbicide ALS inhibitor tribenuron-methyl induced autophagy in *Arabidopsis* seedlings.

It is known, that exogenous branched-chain amino acids reduce the phytotoxic effect of ALS inhibitor herbicides [114]. In addition, in plants with impaired allosteric feedback, which regulates ALS activity by end products of the metabolic pathway, the content of branched-chain amino acids increases, resulting in resistance to ALS-inhibiting herbicides [115]. Therefore, to determine the specific factors that trigger autophagy in plants treated with ALS-inhibiting herbicides, the influence of exogenous branched-chain amino acids on the tolerance of *Arabidopsis* seedlings to tribenuron-methyl and the activation of autophagy in them was investigated [113]. Treatment with tribenuron-methyl led to inhibition of ALS activity and a decrease in the proportion of branched-chain amino acids in the total pool of free amino acids in *Arabidopsis* seedlings. Seedlings treated with exogenous branched-chain amino acids survived after treatment with tribenuron-methyl, whereas the action of the herbicide alone led to the death of seedlings. Immunoblot analysis of proteins showed that the induced accumulation of the ATG8 protein and free GFP returned to basal levels after the addition of exogenous amino acids. The obtained data clearly indicate that activation of autophagy in *Arabidopsis* seedlings is due to a deficiency of branched-chain amino acids, caused of ALS activity blocking by tribenuron-methyl.

To verify the role of autophagy in determining plant tolerance to the action of herbicides ALS inhibitors, the impact of tribenuron-methyl on autophagy-deficient mutants of *Arabidopsis* was investigated [113]. Wild-type and autophagy-deficient *atg5* and *atg7* mutant seedlings were grown

on MS medium for 10 days and then transferred to fresh medium with the addition of 0.05 mg/L tribenuron-methyl or without it (control). In the control, all seedlings had the same biomass and morphology. The addition of tribenuron-methyl to the medium led to a suppression of growth in all types of seedlings, but if the inhibitory effect on wild-type seedlings was 25 %, then the inhibition of growth in mutant seedlings was significantly greater, reaching 45 %. Accordingly, the inhibition of chlorophyll accumulation was higher in mutants. Under the effect of tribenuron-methyl, only a small number of dead mesophyll cells were registered in the vascular tissue of wild-type seedlings. At the same time, the area of dead cells in *atg5* and *atg7* mutants was clearly larger than in the wild type. These results showed that the activation of autophagy contributes to plant tolerance to the action of ALS-inhibiting herbicides.

Accordingly, there are substantial grounds to consider that death of plants under the action of herbicides occurs as a result of inducing one of the PCD types. This means that it is not the herbicide that kills the plant, but rather the plant resorts to suicide due to the action of the herbicide. It is evident that depending on how easily certain damages in the metabolism and physiological systems of plants induce PCD, it can be determined the importance of these systems for the viability of plants, and thus assess the potential of various sites for herbicidal action. However, the question of the involvement of PCD in herbicide-induced pathogenesis cannot be considered definitively settled. Firstly, the data regarding the expression of genes responsible for autophagy [113], were not confirmed by other researchers used transcriptomics for investigation of herbicides action [85, 90, 89]. Secondly, the results obtained in the work [113] imply that under the herbicide influence, autophagy is a process aimed at preserving homeostasis and supporting vitality. Obviously, if this process lasts long enough, it can transform into another type of PCD, and lead to the death of plants [116, 117]. However, the trigger responsible for switching from the «defense» program to the «death» program is still unknown. Nevertheless, there is no doubt that elucidating the mechanism of herbicide-induced pathogenesis, including the involvement of PCD in this process, would provide researchers with a powerful tool to select new sites of herbicidal action.

Despite the uncertainty regarding the mechanism of herbicide-induced pathogenesis, it can be assumed that herbicide effectiveness in inducing this process, and therefore the effectiveness of the herbicide's impact, depends on the intensity and duration of the primary disturbances in plant cells homeostasis caused by the interaction of the herbicide with its site of action. The question arises as to what features of the site of action may determine the intensity and duration of these disturbances. In particular, can the enzyme activity, inhibited by the herbicide, be restored by increasing its expression? To answer this question, it is necessary to clarify how herbicides affect the expression of genes encoding the sites of their action.

The herbicide glyphosate inhibits the enzyme EPSPS in the pathway of biosynthesis of aromatic amino acids (AAA). Studies on the effect of glyphosate on resistant and susceptible biotypes of *A. palmeri* plants showed that in both biotypes, the expression of genes in the pathway of AAA synthesis increases under the influence of glyphosate, and this increase

depends on the herbicide dose. Moreover, glyphosate weakly affected the genes expression in the branched-chain amino acid synthesis pathway (BCAA), and practically did not affect the total enzymes activity in this pathway [118]. In another study, leaf discs of susceptible and resistant (due to EPSPS gene amplification) *A. palmeri* plants were incubated for 24 hours with glyphosate, AAA, or both. In the susceptible population, glyphosate induced the shikimate accumulation and expression of genes in the shikimate pathway. While AAA themselves did not cause any changes, adding them to glyphosate canceled the herbicide's effect on gene expression. These results indicate that in the susceptible population, the absence of the shikimate pathway end products and accumulation of shikimate are signals that induce the expression of genes in the pathway of AAA biosynthesis in response to glyphosate action [119].

The study of *PPO* gene expression in PPO inhibitor-resistant biotypes of *A. palmeri* under the action of the PPO-inhibiting herbicide fomesafen established a 3—6-fold increase in *PPO2* expression compared to the untreated susceptible biotype [120].

The level of *ACC* and *ALS* gene expression in ACC and ALS inhibitor-resistant and susceptible biotypes of ryegrass (*Lolium multiflorum* Lam) was compared in response to the action of ACC inhibitor clodinafop-propargyl, and the ALS inhibitor mesosulfuron-methyl by using quantitative Real-time PCR. It was shown, that in the ACC inhibitor-resistant biotype of ryegrass, after treatment with clodinafop-propargyl, expression of the gene encoding ACC slightly increased compared to the susceptible biotype. At the same time, expression of the gene encoding ALS after treatment with mesosulfuron-methyl did not differ in the resistant and susceptible biotypes [121]. Studying the expression of *ACC* genes in the resistant and susceptible biotypes of barnyardgrass (*Echinochloa crus-galli* (L.) P. Beauv.) showed, that after 6 hours of treatment with ACC inhibitors cyhalofop, fenoxaprop, and pinoxaden, the resistant biotype had significantly higher *ACC* expression compared to the susceptible biotype [122].

Based on the comparative study of *ACC* gene expression levels in resistant and susceptible biotypes, it is difficult to draw a definite conclusion regarding what actually happens after herbicide treatment: whether expression of the *ACC* gene increases in the resistant biotype in response to herbicide action, or if the expression of this gene is suppressed in the susceptible biotype. However, when studying expression level of the *ACC* gene in resistant and susceptible biotypes to the ACC inhibitor quizalofop-ethyl in *E. crus-galli*, it was determined that basal expression level did not differ in both biotypes. After treatment with quizalofop-ethyl, in the resistant biotype the expression level did not change, while in the susceptible biotype, it decreased and practically fell to zero after 8 days of treatment [123]. Somewhat different results were obtained when studying two biotypes of *E. crus-galli*, resistant and susceptible, to the another ACC inhibitor cyhalofop. The basal expression of *ACC1* and *ACC3* genes did not differ in the resistant and susceptible biotypes. However, 24 hours after treatment with cyhalofop, the expression of *ACC1* and *ACC3* genes increased in the resistant biotype, while it decreased in the susceptible biotype, compared to the untreated control [124]. An increase in the expres-

sion of *ACC* genes was observed in the resistant biotype of wild oat (*Avena ludoviciana*) under the action of ACC inhibitor clodinafop-propargyl [125].

The basal expression of the *PsbA* gene in *Commelina communis* biotype resistant to the triazine inhibitor atrazine was approximately 7 times higher than expression of this gene in the susceptible biotype. 24 hours after treatment with atrazine, this excess doubled [126].

The effect of different herbicides on the expression of genes encoding their sites of action was studied in *L. multiflorum* plants. 8 hours after treatment with the ALS inhibitor chlorsulfuron, the expression of the *ALS* gene increased 3 times, while the expression of the *PsbA* gene, encoding the D1 protein, decreased 40 times after treatment with the ET inhibitor atrazine. The expression of the *HPPD* gene practically did not change 8 hours after treatment with the HPPD inhibitor mesotrione [127].

Despite some discrepancies in the above data, their generalization allows the following conclusions to be made. In response to the action of herbicides ALS, ACC, EPSPS and PPO inhibitors, the expression of genes encoding the sites of action of these herbicides may increase in resistant plants. Thus, the level of ALS, ACC, EPSPS, and PPO activity is regulated in plants through negative feedback, the purpose of which is to maintain the necessary content of metabolites vital for the plant. Importantly, this feedback is selective, increasing the expression of the gene, encoding the enzyme whose activity is inhibited by the herbicide. Such negative feedback was not detected under the action of HPPD inhibitor herbicides. For TE inhibitor herbicides a positive feedback was observed — the expression of the *PsbA* gene is inhibited by the action of these herbicides. This corresponds to the data that renewal of D1 protein at the translation step is inhibited by the ROS influence, which content increases due to the blocking of ET by herbicides [128]. It is believed, that relatively low effectiveness of herbicides ET inhibitors is due to the high rate of D1 protein renewal [78]. Perhaps, if it were not for the positive feedback that suppresses the expression of the *PsbA* gene, the effectiveness of herbicides ET inhibitors would be even lower. In plants sensitive to ACC inhibitors, unlike resistant ones, the feedback is positive: under the action of herbicides, the expression of ACC in sensitive plants decreases. This may be explained by the fact that ACC expression is associated with proliferative activity, as its highest level is observed in meristems [129]. If cell proliferation decreases or even stops in sensitive plants as a result of herbicide action, then, accordingly, ACC expression may also decrease.

From the above data, it can be concluded that the intensity and duration of primary disturbances as a result of the herbicide interaction with the site of its action may depend on the nature of the feedback loops that regulate the expression of genes encoding these herbicides sites of action. When considering the characteristics of the most effective classes of modern herbicides, it can be seen that they exhibit specific features of feedback loops. The most effective classes of herbicides include those, whose effective dose does not exceed a few tens of grams per hectare. This criterion corresponds to herbicides from the classes of synthetic auxins, inhibitors of ALS, PPO and HPPD. The phytotoxic action of synthetic auxins is characterized by being directly caused by the failure of the negative feedback regulating the expression of auxin-dependent genes [130]. This feedback is adapted for

endogenous auxin, which concentration in plant cells is tightly controlled. When herbicides from the class of synthetic auxins are applied, their concentration in cells can persist at a level significantly higher than the concentration of endogenous auxin for quite some time. As a result, the negative feedback intended to halt the expression of auxin-dependent genes does not trigger, leading to the disorganization of the phytohormonal regulation system and plant death.

As mentioned earlier, the high effectiveness of herbicides ALS inhibitors is due to the fact that inhibition of ALS activity by the herbicide is accompanied by the breakdown of thiamine diphosphate, which is a cofactor, necessary for this enzyme functioning [74]. Since under normal conditions, the amount of cofactor should not significantly change, it is evident that in plants, there is no system to control its content, and accordingly, there is no negative feedback that would ensure the restoration of the cofactor content. Therefore, despite the presence of a feedback loop that could lead to increased ALS expression, the enzyme's activity cannot be restored due to the absence of the cofactor.

The biosynthesis of carotenoids is blocked by herbicides that are inhibitors of phytoene desaturase, and HPPD inhibitors, which inhibit the synthesis of plastoquinone, a cofactor of phytoene desaturase. Moreover, the effectiveness of HPPD inhibitors is greater than that of phytoene desaturase inhibitors. The literature available to us lacks data on the influence of herbicides on the expression of genes encoding phytoene desaturases. At the same time, under the action of HPPD inhibitors, the expression of the gene encoding this enzyme remained unchanged [127]. Obviously, just like in the case of thiamine diphosphate, under normal conditions, the content of plastoquinone, which is an electron carrier in the PS II of chloroplasts and a cofactor of phytoene desaturase, should not change significantly. Therefore, its content is not controlled, and accordingly, there is no negative feedback that would allow compensating for the losses of plastoquinone by increasing the expression of the gene encoding HPPD.

Thus, it can be concluded that, if the herbicide action is due to the deficiency of certain metabolites, the absence of negative feedback, aimed at restoring the content of this metabolite by increasing expression of the gene, encoding the site of herbicide action, is a necessary requirement for high efficiency of this herbicide. The opposite situation is observed in the case of PPO-inhibiting herbicides, the phytotoxicity of which is caused by the rapid accumulation of protoporphyrinogen, which is the substrate of the enzyme inhibited by the herbicide. Blocking the PPO activity inhibits the synthesis of both chlorophyll and heme. Heme is a regulator of the porphyrin synthesis pathway, therefore inhibition of heme synthesis causes a sudden increase in the flow of carbon in the way of porphyrin synthesis and, accordingly, a sudden accumulation of protoporphyrinogen [131]. In the case of PPO inhibitors, in contrast to ALS and HPPD inhibitors, a negative feedback, that causes the accumulation of the substrate of the enzyme inhibited by the herbicide, is a necessary condition for the high effectiveness of the herbicidal action.

In conclusion, based on the analysis of data on the mechanism of herbicide-induced pathogenesis and information on the peculiarities of the sites of action of the most effective classes of herbicides, it is possible to

identify research directions that should develop criteria for selecting new sites of herbicides action and roughly outline these criteria as follows.

Firstly, the study of herbicide-induced pathogenesis mechanisms, including the participation of PCD in this process, will allow the development of methods to assess how important a particular metabolic pathway or physiological system is for the plant's vital activity. Accordingly, it will be possible to determine the extent to which disturbances in their functioning can ensure high efficiency of herbicidal action.

Secondly, the study of mechanisms supporting plant organism homeostasis will allow the development of clear criteria for selecting potential herbicide action sites. At present, when choosing a specific enzyme as herbicide action site, it can be used the following characteristics of this enzyme. It is logical to assume that for high herbicidal activity, the content of the enzyme, chosen as the action site, should be low [75]. In addition, the rate of enzyme turnover should not be high.

Despite the insufficiently studied mechanisms of maintaining homeostasis, information about the presence of feedback loops that regulate the expression of the selected enzyme can be taken into account when choosing this enzyme as a site of herbicide action. If it is expected that herbicidal action will be caused by a deficiency of products of the metabolic pathway to which this enzyme belongs, the negative feedback that could lead to increased expression of this enzyme should be absent. This requirement can be implemented if the enzyme catalytic activity requires the presence of cofactors, and the herbicide action leads to their deficiency. A more complex way to implement this requirement lies in the fact that the consequences of herbicide action hinder the expression of the gene encoding its site of action. In this case, a positive feedback loop arises, which strengthens the inhibitory effect of the herbicide. In the case when the herbicidal action is caused by the accumulation of a phytotoxic metabolite that is a substrate of the herbicide-inhibited enzyme, the negative feedback loop will favor the action of the herbicide, but it should be directed not at expression of the enzyme which is the site of action, but at the enzymes preceding it.

It should be recognized, that the mentioned research areas are not in the center of attention of the experts in the field of herbology and weed control. The terms «induced pathogenesis», «programmed cell death», «feedback» are not often found in the titles of articles in weed science related journals [132]. However, in our opinion, studying the mechanisms of herbicide-induced pathogenesis, in particular the PCD participation in this process, as well as the study of feedback loops, that support plant cell homeostasis, will allow to obtain the magic key that will open the way to creating herbicides with new mode of action and solving the problem of weed resistance to herbicides.

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ЧОГО НЕ ВИСТАЧАЄ ДЛЯ РОЗРОБКИ НОВИХ ГЕРБІЦИДІВ І ВИРІШЕННЯ ПРОБЛЕМИ РЕЗИСТЕНТНОСТІ?

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Розглянуто проблему резистентності бур'янів до гербіцидів та можливі шляхи її розв'язання. Обговорюються альтернативні хімічному методи контролювання бур'янів. Зроблено висновок, що впровадження альтернативних методів дасть змогу зменшити роль гербіцидів у інтегральних технологіях захисту посівів, проте повна відмова від застосування гербіцидів є малоймовірною. Водночас проблема резистентності потребує істотного вдосконалення хімічного методу, насамперед внаслідок зменшення спрямованості селекційного тиску гербіцидів. Констатується, що найефективнішим засобом боротьби з резистентністю є комплексне застосування гербіцидів з різними механізмами фітотоксичності. Обговорюються вимоги до антирезистентних

композицій гербіцидів. Зазначається, що сучасний асортимент гербіцидів обмежує можливість вибору партнерів для створення таких композицій. Зроблено висновок, що для боротьби з резистентністю необхідна розробка нових ефективних гербіцидів з відмінними від існуючих механізмами фітотоксичності. Розглядаються методи пошуку нових сайтів дії гербіцидів і причини незадовільної ефективності їх реалізації. Обґрунтовується думка, що для визначення критеріїв вибору нових сайтів гербіцидної дії необхідно розкрити механізми індукованого гербіцидами патогенезу й обговорюються дані щодо участі програмованої загибелі клітин у цьому процесі. Іншим важливим напрямом досліджень, необхідним для визначення критеріїв вибору перспективних сайтів гербіцидної дії, є вивчення зворотних зв'язків, які регулюють функціонування метаболічних шляхів та фізіологічних систем рослин. Аналізуються особливості функціонування зворотних зв'язків, які контролюють експресію генів, що кодують різні сайти дії найефективніших класів гербіцидів.

Ключові слова: гербіциди, резистентність, нові сайти дії, індукований патогенез, програмована загибель клітин, зворотні зв'язки.

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