

THE MORPHO-PHYSIOLOGICAL TRAITS IN SOME SOFT WHEAT CULTIVARS WITH DIFFERENT TOLERANCE TO SALINITY AND COLD

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ABSTRACT

The soft wheat *Triticum aestivum L.* is one of the oldest cultivated plants, one of the most widespread and produced crops in the largest quantity. The structure of cultivars in Albania has changed from time to time. Wheat stands out for its high ecological adaptability, which is expressed in its growth in very different climatic and soil conditions. However, wheat gives the highest yield only when there is a complete match between its biological requirements and ecological conditions. The experiment was carried out during the 2021-2022 agricultural season, at the Experimental Didactic Farm (EDF) of the Agricultural University of Tirana (AUT). The object of the study was seven soft wheat cultivars with different tolerance to salinity and cold. The aim of the study was comparing different soft wheat cultivars, part of wheat cultivar structure in Albania, for some flag leaf biometric traits, harvest index and grain production. The analyze of variance of the data showed that among the wheat cultivars included in the study there are significant differences for the flag leaf traits, for the values of harvest index and the imbibition potential too. The cultivar *Kraljica*, known for its cold tolerance, resulted in high biomass production, grain production and a high 1000 grains weight. Cv. *Vittorio*, resistant to cold, water stress and medium tolerant to salinity, resulted in low biological mass, narrow leaf angle, low harvest index, but high 1000 grains weight. Cv. *Nogal*, known as salt sensitive and high protein content, resulted in smaller leaf width and especially higher imbibition. Cv. *Dajti*, with medium resistance to cold and tolerant to salinity, resulted in wider leaf angle, small biomass but high harvest index.

Keywords: Abiotic stresses, flag leaf parameters, harvest index, imbibitions, wheat cultivars

1. INTRODUCTION

Agriculture in the 21st Century is facing a frightening challenge of achieving nearly a 70% increase in crop productivity by year 2050 (Joshi et al. 2016). FAO (2009) also has predicted an increase of least 50% in food production to meet the future demand. Wheat is one of the most widespread and produced crops in the largest quantity. It serves as a main food for more than 2.5 billion peoples in the world. The biggest grain producers are China, India, Russia, USA, Canada, France and Ukraine (FAO, 2020). In recent years, wheat grain requirements of developing countries have increased. Even if wheat breeding may impact positively the yield potential, the success of the future depends on the collaboration between wheat breeders and crop physiologists (Watson D.J., 1953; Jackson et al., 1996). More than 90% of crop biomass is derived from photosynthetic products (Zelitch 1979). It was reported that a genotype with improved photosynthetic activity under stress conditions could produce more biomass, suggesting that improving photosynthetic adaptation to environmental conditions will help to enhance crops biomass production (Krieg 1983; Khadaka, et al., 2020). Plants, unlike animals, are sessile. Those demands, those adverse changes in their environment, are quickly recognized, distinguished and responded to with suitable reactions. Drought, heat, cold and salinity are among the major abiotic stresses that adversely affect plant growth and productivity (Shanker, A., 2022). Salinity and cold stress often constrain the growth and productivity of main crop species such as wheat. Wheat stands out for its high ecological adaptability, which is expressed in its growth in very different climatic and soil conditions. However, wheat gives the highest yield only when there is a complete match between its biological requirements and ecological conditions. The structure of cultivars in Albania has changed from time to time (Kashta et al., 2010). More and more new wheat cultivars are introduced from abroad. This study was conducted to evaluate some morpho-physiological traits of wheat cultivars with different tolerance of salinity (Bacu, A. et al., 2020) and cold, to determine the relationships of these traits with grain yield in soft wheat under the Mediterranean conditions, and to advise on genotypes to be used as salinity and cold tolerant in wheat breeding programs.

MATERIAL AND METHODS

Seven soft wheat cultivars (*Dajti*, *UBT-2*, *Kraljica*, *Frenetic*, *Nogal*, *Vittorio*, *Artico*) have been compared for seeds imbibition capacity in laboratory conditions, flag leaf parameters in flowering and grain production

in field. The experiment was carried out during the 2021-2022 agricultural season, at the Experimental Didactic Farm (EDF) of AUT in Valias, Tirana. It was set up based on a randomized block scheme with four replications for each cultivar. One repetition extends over an area of 10 m², i.e. 4 m long and 2.5 m wide. Different morpho-physiological and production evaluations have been performed by very common field measurements without sacrificing the plants. Variance analysis and correlation analysis were performed on the data for each evaluated parameter.



Photo 1. Views from the wheat field experiment at EDF, Valias.



Photo 2. Different moments of work at wheat experimental field.

RESULTS AND DISCUSIONS

Graphics and tables below represent the results of data processing for all parameters and for each wheat cultivar including in the study; seeds imbibition capacity (Fig.1), flag leaf length, width, leaf area and leaf angle (Fig.2), biological production, grain production, 1000 grains weight and

harvest index (Fig. 3). The variance analysis show that for all parameters mentioned above, the found differences between cultivars are statistically verified (Table 1). The results of the correlative analyzes among evaluated different traits are given in Table 2.

The seeds imbibition capacity

The minimum moisture content for wheat seeds germination is 35-45% of the dry weight of the grain. After receiving water, the seed increases in volume and weight and the activation of hormones (GA) and the hydrolytic enzymes occurs (Ibro, V. et al, 2019). Wheat cultivars taken in consideration in the laboratory test related their seeds imbibition capacity, showed significant differences, where the cultivars *Nogal*, *Artico* and *Dajti* stand out as the most powerful in water absorption for large seeds, while *Nogal* and *Vittorio* for small ones. It's very evident the big difference in seeds imbibition among two local wheat cultivars *Dajti* and *UBT-2*, results that need more attention in future research.

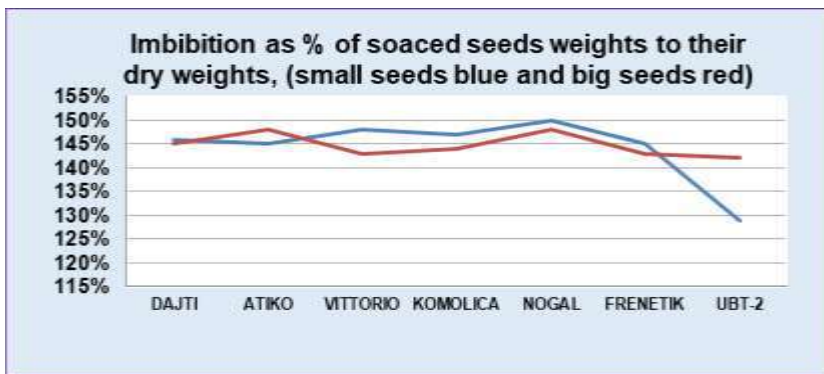


Figure 1. Imbibition capacity as % of soaked seeds weights to their dry weights, (small seeds blue and big ones red).

Flag leaf parameters

The flag leaf parameters evaluated were leaf length, leaf maximal width, leaf area and leaf angle (the angle between flag leaf and stem). Leaf area parameters in the flowering are important for yield components and have their effects on wheat yield. The determination of the leaf area in flowering, generally, shows the development of the source capacity and can be used as a parameter for the selection of wheat lines in the field (Barjevic and Williams 1982). The graphics below show the results of ANOVA analyzes for each of them.

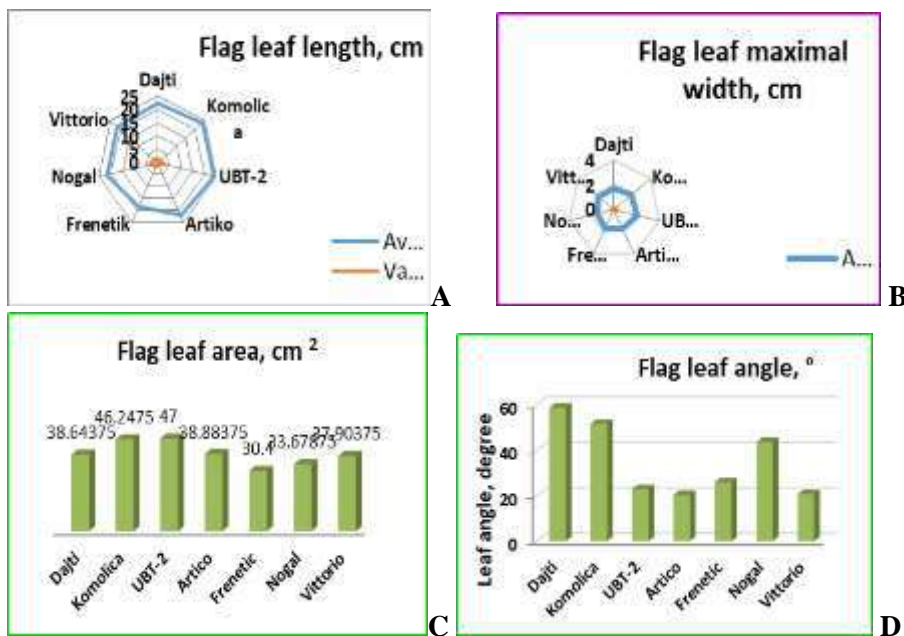


Fig. 2: The flag leaf parameters of seven soft wheat cultivars, EDF 2021. **A, B** and **C** graphics show particularly the length, maximal width and area of flag leaf in flowering phase. The graphic **D** shows the mean values of full expanded flag leaf angle.

The above results, given in graphics **A, B** and **C**, show that cv.*UBT-2* and cv. *Kraljica* have the bigger leaf length, width and area. On the other side, cv. *Frenetik* and cv. *Nogal* have the smallest ones. Cv. *Dajti* and cv. *Nogal* have long, but narrow leaves. Many authors since years '80 (Briggs 1980; Barjevic and Williams 1982; Ibro 1988; 1991) have underlined the very important role of flag leaf photosynthesis during grain filling.

The graphic **D** shows the values of flag leaf angle (the value in degrees of the angle between leaf and stem). Several authors reported the leaf angle as an important factor of plant density and grain yield (Duncan 1974; Ibro 1996). The cultivars *Artiko*, *Vittorio* and *UBT-2* have the narrowest flag leaf angles and cv. *Dajti* and cv. *Kraljica* have the widest ones.

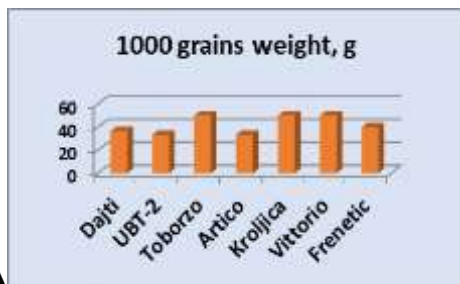
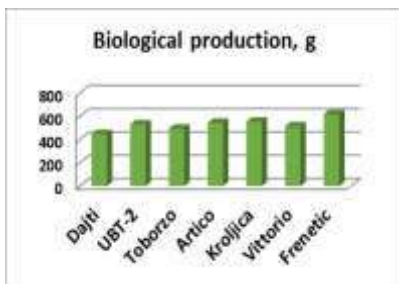
Table 1. The average values of flag leaf evaluated parameters.

	Leaf angle, degree	Leaf max width, cm	Leaf length, cm	Flag leaf area cm ²
Dajti	58.625	1.7075	22.3	38.64375
Kraljica	51.575	1.9225	23.8375	46.2475
UBT-2	22.925	2.1075	24.1375	47
Artico	20.3	1.735	22.3375	38.88375
Frenetic	25.925	1.6325	18.3875	30.4
Nogal	43.525	1.535	21.7625	33.67875
Vittorio	20.7	1.7225	21.7125	37.90375

Wheat production traits

The wheat production traits like biological production (PB), grain production (GP) and harvest index (HI) importance was showed from many authors (Donald, Hamblin 1976; Evans and Wardlaw 1976; Ibro 1988).

The data processing results regarding production indicators as biological production (PB) are given in Figure 3A. The highest ones were found in cultivars *Frenetic*, *Kraljica* and *Artico*, while the lowest in cultivar *Dajti*. The graphics in the Figure 3.B show that the cultivars *Frenetic*, *Artico* and *Kraljica* gave the highest grain production. The graphics in Figure 3.D show that the highest harvest index (HI) was found for the cultivar *Artico*, *Frenetic* and *Dajti* and the lowest one for the cultivar *Vittorio*. The highest 1000-grain weight was found in cultivars *Toborzo*, *Kraljica* and *Vittorio* (Figure 3.C).



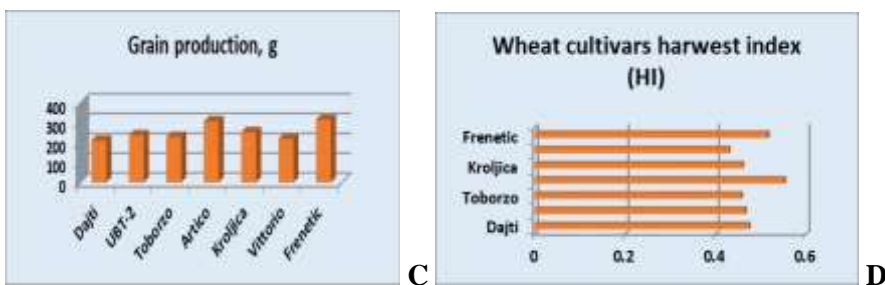


Figure 3. Wheat cultivars production parameters, EDF 2021.

The results of variance analyzes for every production traits evaluated on wheat cultivars are given in the Table 2.

Table 2. The results of variance analyzes of evaluated wheat production traits.

Production Parameters	Source of Variation	SS	df	MS	F	P-value	F crit
BP	Between Groups	50418.4762	6	8403.07937	3.46307926	0.02599567	2.847726
GP	Between Groups	32332.5714	6	5388.7619	8.80037328	0.00042663	2.847726
P1000	Between Groups	1123.80952	6	187.301587	13.11111111	4.8724E-05	2.847726
HI	Between Groups	0.03096169	6	0.00516028	6.30255741	0.00220985	2.847726

Table 3. The values of correlation coefficients between wheat cultivars production parameters, EDF 2021.

	BP	GP	W 1000	HI
BP	1			
GP	0.84			
W 1000	-0.03	-0.34		
HI	0.44	0.85	-0.66	1

From the results of correlation analysis between different production indicators, given in the table above, high positive correlations were found between grain production (GP) and the harvest index (HI), as well as grain production (GP) and biological production (BP).

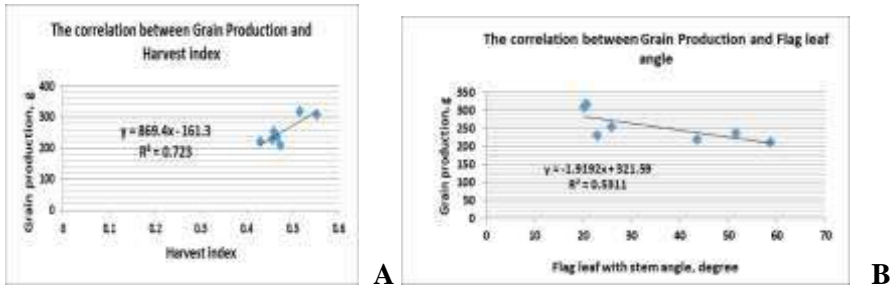


Fig. 4. The graphic presentations of the correlation between Grain Production and Harvest index (A) and the correlation between Grain Production and Flag leaf angle (B) at seven wheat cultivars taken in consideration.

CONCLUSIONS

From the data processing, as well as the discussion of the results found for all parameters included in the study, can reach to the following conclusions:

Among the wheat cultivars included in the study, there are statistically proven differences both for biometric traits and for grain production indicators.

Cultivar *Kraljica*, known for cold tolerance, resulted in high biomass production, grain production and high 1000 grains weight.

Cultivar *Vittorio*, resistant to cold, water stress and medium tolerant to salinity resulted in low biological mass, narrow leaf angle, low harvest index, but high P1000.

Cultivar *Nogal*, known as salt sensitive and high protein content, resulted in smaller leaf width and especially higher seed imbibition.

Cultivar *Dajti*, with medium resistance to cold and salt tolerance, resulted in wider leaf angle, small biomass but high harvest index.

As related to the other three wheat cultivars, for *Artico* and *Frenetic*, high biomass and grain production and relatively narrow leaf angle were found, while for the cultivar *UBT-2* relatively higher parameters (length, width and leaf area) of the flag leaf were found, but narrow leaf angle. Since there is little information on their resistance to abiotic stresses, it is recommended to continue with additional studies for this purpose.

Based on the above, we recommend wheat producers to take into consideration the relevant conclusions during the selection of the wheat cultivar and cultivation technologies.

REFERENCES

Bacu, A., V. Ibro, M. Nushi. (2020): Compared salt tolerance of five local wheat (*Triticum aestivum L.*) cultivars of Albania based on morphology, pigment synthesis and glutathione content. *Euro Biotech Journal volume 4 issue 1. January 2020 p. 42-52.*

Barjevic, S., W.A. Williams (1982): Genotypes environment influence on leaf area parameters and yield components and their effects on wheat yield. *Crop. Sci.*, 22: 1020-1025

Brigg, S. (1980): Relationship between morphological characteristics of the flag leaf and grain yield in spring wheat. *Crop. Sci.*, 351-355.

Duncan W.G (1974): Leaf angles, leaf area and canopy photosynthesis. *Agron. J.* 60,422-424

Evans, L.T. (1997): Adapting and improving crops: the endless task. *Philos. Trans. R Soc Lond Biol. Sci.* 352: 901-906.

Evans, L. T., Wardlaw I. W. (1976): Comparative physiology of grain yield in cereals. *Adv. Agron.* 28,301-361.

Ibro, V. (1988): Study of some indicators related to photosynthesis and wheat production. Dissertation.

Ibro, V. (1991): Vlerësimi i disa treguesve fiziologjikë në linjat e grurit të butë. *Buletini i Shkencave Bujqësore* 3, 9-14.

Ibro, V. (1996): Këndi gjethor një tregues i rëndësishëm për seleksionimin dhe teknologjinë e grurit. *Përmirësimi Gjenetik dhe Prodhimi i Farave dhe fidaneve në Shqipëri. f.* 62-65.

Jackson et al., (1996): *J. Sci. Food Agric.*, 71 (1): 103-110.

Joshi et al., (2016): *Int. J. Sci. Res.*, 5 (6): 1798-1802.

Krieg, D.R. (1983): Photosynthetic activity during stress. *Agricultural Water Management. Vol.7, issues1-3, p.249-263. ISSN 0378-3774.*

Khadaka, K. et al. (2020): A physio- morphological trait based approach for breeding drought tolerance wheat. *Medicine Biology- Frontiers in Plant Sciences.*

Shanker, A. (2011): Abiotic Stress Response in Plants - Physiological, Biochemical and Genetic Perspectives. 358 p.

Watson D.J. (1953): The physiological basis of variation in yield. *Adv. Agron.* 4, 101-148.

Zelitch I. (1979). Photosynthesis and plant productivity. *Chem. Ing. News.* 57, 28-48.

Agroelita-Sh.p.k., AUTUMN WHEAT, <https://www.agroelita-shpk.com/autumn-wheat/>

AGROSERVICE S.p.A, Bread Wheat Vittorio http://www.agroservicespa.it/en/prodotti/view/vittorio_frumento_tenero_eng.html

AXEREAL Serbia, Nova ozima pšenica odlične rodnosti i vrhunskog kvaliteta, <https://www.axereal.rs/sites/default/files/2021-10/3.FRENETIC.pdf>

AXEREAL Serbia, Rana pšenica stabilnog prinosa i visokog sadržaja proteina , https://www.axereal.rs/sites/default/files/2021-10/5.NO GAL_.pdf

Vemi select, Kraljica, <http://agromasterseeds.com/en/product/kraljica/>.

ZINC CROSSTALK WITH SIGNALING PATHWAYS AT A GLANCE

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ABSTRACT

For the first time, zinc (Zn) was identified as a critical micronutrient in 1869 while studying the growth of the fungus *Aspergillus niger*. Subsequently, it was confirmed as such in both the plant and animal kingdoms. Over the years a substantial body of research has demonstrated that the deficiency of zinc in the organism, either due to low dietary intake or impaired absorption in the intestine, leads to abnormal development during embryonic stages and affects the nervous system, hormonal balance, immune system, digestive system, and vascular system in adults. Throughout the lifespan of a living cell, zinc levels fluctuate within a physiological concentration range, playing a crucial role in protein stability and enzyme activity. Extensive work has been conducted in an attempt to elucidate the potential crosstalk between cellular zinc and various signaling pathways. In this review, we provide an overview of the crosstalk between zinc and several signaling pathways, with a particular focus on proliferation and apoptosis.

Keywords: signaling pathways, reactive species, apoptosis, proliferation

Historical perspective on zinc-related research

Vallee and Falchuk (1993) showed that the lack of zinc (Zn) in the organism, either due to low dietary intake or impaired absorption from the intestine, leads to abnormal development during the embryonic stages and affects various systems in adults, including the nervous system, hormonal balance, immunity system, digestive system, and vascular system. These multifaceted interactions of Zn are associated with its presence in nearly every compartment of the cell. While the majority of cellular Zn is distributed throughout the cell, including the nucleus and organelles, only low levels are associated with cell membranes. Studies have shown that most Zn circulates within the cell bound to proteins and anionic complexes (Beyersmann and Haase 2001). Cellular Zn can modulate the activity of phosphodiesterases (PDEs) in a concentration-dependent manner. Specifically, higher concentrations of Zn lead to the activation of the enzyme, while lower concentrations have an inhibitory effect. This phenomenon has been demonstrated through investigations of the binding affinity of cGMP and cAMP to their respective PDEs (Omburo *et al.*, 1995; Kovala *et al.*, 1997). Conversely, cGMP can inhibit Zn uptake, although the underlying mechanism is not yet fully understood (Haase 2001).

There have been some controversies surrounding the effect of Zn on mitogen-activated protein kinases (MAP kinases). The deficiency of Zn in human and rat cells has been shown to result in a decrease in insulin-like growth factor 1 (IGF-1) and its corresponding gene expression. However, in rat fibroblasts, the phosphorylation levels of IGF-1/2 receptor and its substrates remain unaffected despite alterations in Zn concentration (MacDonald 2000).

Conversely, higher Zn concentrations have been found to stimulate the phosphorylation of protein kinases and the activity of MAP kinases (Hansson 1996; Wu *et al.*, 1999). Among the initial substrates of MAP kinases affected by Zn concentration are Jun and ATF-2, mediated through the activation of ERK, JNK, and p38 (Samet *et al.*, 1998). Additionally, Zn can stimulate the PI3K (phosphatidylinositol 3-kinase) pathway (Kim *et al.*, 2000).

Zinc interference with cell cycle transition

Zinc (Zn) was initially identified as a critical micronutrient in 1869 during the study of the growth of the fungus *Aspergillus niger* and was later confirmed as such in both the plant and animal kingdoms (Prasad 1993). For a considerable time, it was widely accepted that Zn played a pivotal role in cell

proliferation. The absence of Zn interfered with DNA replication by preventing thymidine incorporation, underscoring its importance in the G1/S transition (Chesters *et al.*, 1989).

In subsequent years, studies revealed that the absence of Zn could be a limiting factor for transitioning into the S phase until the restriction point in mid-G1. Once the cell overcame this restriction point, it became committed to progressing into the next phase of the cell cycle, regardless of the presence or absence of Zn. In 1999, Chesters and Petrie further elucidated that Zn was required for cells to reenter the G1 phase after completing mitosis (Chesters and Petrie 1999).

The application of modern techniques allowed for the observation of individual cells and their behavior when deprived of only Zn but in the presence of necessary mitogens. Under these specific circumstances, circulating cells faced two possibilities: they could either exit the cell cycle and enter quiescence or stall in the S phase. In cases where the latter occurred, the cell was capable of completing one cycle in the absence of Zn and then reentering the next G1 phase. However, the final S phase was characterized by significantly reduced rates and efficiency, leading to a higher accumulation of DNA damage (Maria *et al.*, 2020).

Among the entities susceptible to Zn deprivation were p53 and AP1, two transcription factors crucial for DNA repair mechanisms (Ho and Ames 2002; Yan *et al.*, 2008). When cells chose the path of entering quiescence, they exhibited hypoactivity of CDK2, less DNA damage accumulation, and inactivation of p21 (Maria *et al.*, 2020). This cell cycle profile contrasted with naturally occurring quiescence, where cells accumulated extensive DNA damage and displayed high p21 activity (Arora *et al.*, 2017; Barr *et al.*, 2017), confirming that Zn deprivation was the key factor inducing quiescence. The reintroduction of Zn empowered quiescent and S-phase cells to resume their progression through the cell cycle (Maria *et al.*, 2020).

Zn – MAPK signaling pathway

Considerable evidence now supports the idea that zinc (Zn) levels within living cells fluctuate within physiological concentrations (Yamasaki *et al.*, 2007; Kim *et al.*, 2011; Vergnano *et al.*, 2014; Que *et al.*, 2015; Sanford and Palmer, 2020). Zn primarily serves as a vital biological cofactor, playing a pivotal role in protein stability and enzyme activity (McCall *et al.*, 2000).

In the past year, extensive research has been conducted to elucidate the potential crosstalk between cellular zinc and various signaling pathways. One of the initial interactions discovered was with the calcium (Ca) signaling pathway, where higher concentrations of Zn in the cytosol induced a release of

calcium from the endoplasmic reticulum (ER), and vice versa (Qin *et al.*, 2011).

Anson *et al.*, (2021) demonstrated that, under specific conditions, an increase in Zn concentration within the low micromolar range (40 μM) had no effect on cytosolic Ca levels. During their investigation, they monitored the activation of the mitogen-activated protein kinase (MAPK) pathway and observed increased phosphorylation of extracellular signal-regulated kinase (ERK) in a Zn-specific manner, primarily through the activation of Ras. This activation did not occur by blocking ERK-directed phosphatases, as was previously believed (Ho *et al.*, 2008).

Based on their findings, Anson *et al.*, (2021) hypothesized that Zn influx might directly activate Ras, leaving its main upstream activator, the epidermal growth factor receptor (EGFR), untouched. This could potentially lead to the phosphorylation of Akt, possibly via phosphoinositide 3-kinase (PI3K). Importantly, this new hypothesis is supported by the fact that Zn administration was conducted under strict conditions involving low concentrations in the range of nanomolar and low micromolar levels, which do not activate stress response signaling pathways, apoptosis pathways, or induce toxicity.

Redox signaling and zinc's role

The definition of redox signaling has undergone multiple revisions by different researchers. However, they all agree on two crucial components: the reactive species involved and the stimulated reactions or pathways. Many well-characterized signaling pathways within cells rely on specific second messengers during their signal transduction. Redox pathways share this characteristic but have a key difference—the secondary messengers in redox signaling can oxidize other molecules not originally part of the redox cascade, sometimes independently of any signaling pathway (Pillay *et al.*, 2016).

In most cases, redox reactions induce the oxidation or reduction of cysteine residues. Another notable feature of these reactions is the distance between the reactive species and their target. Peroxides such as H_2O_2 , O^- , and OH^- are the most important and well-characterized secondary messengers in redox pathways (Forman *et al.*, 2014). Studies have demonstrated instances where zinc serves as a secondary messenger and cases where zinc acts as an inhibitor of cysteine oxidation (Maret and Vallee 1998). During the oxidation of target proteins, also known as redox transducers, zinc ions may be released, affecting other proteins involved in various cellular pathways such as apoptosis or proliferation.

One of the transcription factors affected by zinc is Nrf2 (nuclear factor erythroid 2-related factor 2), which, under stress conditions, controls the

transcription of antioxidative compounds within the cell (Itoh *et al.*, 1997; Kansanen *et al.*, 2013). In the presence of reactive species, zinc ions can alter the molecular structure of Nrf2 repressor Keap1, leading to increased stability of the transcription factor (McMahon *et al.*, 2018).

Phosphatases represent another group of proteins that can be targeted for inhibition by zinc. Based on the type of amino acid phosphorylated, phosphatases are divided into three specific groups: 1- PTP (protein tyrosine phosphatase); 2- PSP (protein serine/threonine phosphatase); and 3- DUPS (dual-specificity phosphatase). Among the PTPs inhibited by zinc, even at very low concentrations (nanomolar), is PTEN (phosphatase and tensin homolog), which acts as a tumor suppressor by inhibiting PIP3 (phosphatidylinositol-3,4,5-triphosphate), which, in turn, activates Akt. Consequently, zinc indirectly induces survival mechanisms and proliferation (Yang and Arrizabalaga 2017). An example of zinc regulation in PSPs is the direct binding of zinc with PP2A and lambda serine/threonine PSPs. Both of these enzymes are involved in several signaling pathways that lead to cell proliferation, cell death, and lipid metabolism (Zhuo and Dixon 1997; Seshacharyulu *et al.*, 2013).

Regenerate Abnormalities in zinc physiology

Alterations in zinc concentration beyond the physiological range can significantly influence various cellular processes, spanning from proliferation and metabolism to chronic inflammation and the impairment of the immune system, leading to systemic disorders. Non-physiological zinc levels directly disrupt the redox equilibrium, shifting it toward the pro-oxidative side and resulting in an increase in reactive species and total reactive oxygen species (ROS). These elevated ROS levels can interfere with the nuclear translocation of two transcription factors, STAT 1 and 3, thereby inhibiting gene transcription in neurons and causing abnormal brain development (Supasai *et al.*, 2017). Oxidative stress induced by zinc deficiency has been observed to decrease cell proliferation by reducing the activity of ERK1/2. Additionally, it has been shown that the activity of JNK, p38, and AP-1 is increased under these conditions (Zago *et al.*, 2005).

CONCLUSION

Zinc plays a crucial role in signal transduction and is implicated in pathways that lead to proliferation, cell survival, and apoptosis. Moreover, zinc homeostasis helps maintain the delicate balance between prooxidative and antioxidative molecules, thereby protecting cells from the damaging effects of reactive oxygen species. However, when zinc levels deviate beyond

the physiological range, it has been demonstrated to induce oxidative stress and potentially premature cell death (Huebner and Haase 2021). Despite extensive evidence regarding zinc's role in numerous cellular processes under both normal and abnormal conditions, there is still a need for further research to better elucidate the physiological significance of zinc crosstalk.

REFERENCES

Kim AM, Bernhardt ML, Kong BY, Ahn RW, Vogt S, Woodruff TK, O'Halloran TV. 2011. Zinc sparks are triggered by fertilization and facilitate cell cycle resumption in mammalian eggs. *ACS chemical biology*, **6**: 716-23. doi:10.1021/cb200084y.

Anson KJ, Corbet GA, Palmer AE. 2021. Zn²⁺ influx activates ERK and Akt signaling pathways. *Proceedings of the National Academy of Sciences of the United States of America*, **118(11)**: e2015786118.

Arora M, Moser J, Phadke H, Basha AA, Spencer SL. 2017. Endogenous replication stress in mother cells leads to quiescence of daughter cells. *Cell Reports*, **19**:1351–1364.

Barr AR, Cooper S, Heldt FS, Butera F, Stoy H, Mansfeld J, Nova k B, Bakal Ch. 2017. DNA damage during S-phase mediates the proliferation-quiescence decision in the subsequent G1 via p21 expression. *Nature Communications*, **8**:14728.

Beysmann D, Haase H. 2001, Functions of zinc in signaling, proliferation and differentiation of mammalian cells. *Biometals*, **(3-4)**:331-41.

Yang C, Arrizabalaga G. 2017. The serine/threonine phosphatases of apicomplexan parasites *Molecular microbiology*, **106 (1)**: 1–21.

Pillay CS, Eagling BD, Driscoll SRE, Rohwer JM. 2016. Quantitative measures for redox signaling. *Free radical biology and medicine*, **96**:290–303.

Chesters JK, Petrie L, Vint H. 1989. Specificity and timing of the Zn²⁺ requirement for DNA synthesis by 3t3 cells. *Experimental Cell Research*, **184**:499–508.

Chesters JK, Petrie L. 1999. A possible role for cyclins in the zinc requirements during G1 and G2 phases of the cell cycle. *The Journal of Nutritional Biochemistry*, **10**:279–290.

Hübner Ch, Haase H. 2021. Interactions of zinc- and redox-signaling pathways. *Redox biology*, **41 (2021)**: 101916. doi:10.1016/j.redox.2021.101916.

Kansanen E, Kuosmanen SM, Leinonen H, Levonen A-L. 2013. The Keap1-Nrf2 pathway: mechanisms of activation and dysregulation in cancer. *Redox Biology*, **1**: 45–49.

Que EL, Bleher R, Duncan FE, Kong BY, Gleber SC, Vogt S, Chen S, Garwin SA, Bayer AR, Dravid VP, Woodruff TK, O'Halloran ThV. 2015. Quantitative mapping of zinc fluxes in the mammalian egg reveals the origin of fertilization-induced zinc sparks. *Nature chemistry*, **7(2)**: 130-139. <https://doi.org/10.1038/nchem.2133>.

Forman HJ, Ursini F, Maiorino M. 2014. An overview of mechanisms of redox signaling. *Journal of molecular and cellular cardiology*, **73**:2–9. doi:10.1016/j.yjmcc.2014.01.018.

Haase H. 2001. Zinkhomöostase in Säugerzellen: Untersuchungen zur Aufnahme, intrazellulären Verteilung und Toxizität. *GCAVerlag, Herdecke*, ISBN 3-89863-024-2.

Hansson A. 1996. Extracellular zinc ions induce mitogen-activated protein kinase activity and protein tyrosine phosphorylation in bombesin-sensitive Swiss 3T3 fibroblasts. *Archives of biochemistry and biophysics*, **328** (2): 233-8. doi:10.1006/abbi.1996.0168.

Ho E, Ames BN. 2002. Low intracellular zinc induces oxidative DNA damage, disrupts p53, NFkappa B, and AP1 DNA binding, and affects DNA repair in a rat glioma cell line. *Proceedings of the National Academy of Sciences of the United States of America*, **99** (26): 16770-5. doi:10.1073/pnas.222679399.

McCall KA, Huang C, Fierke CA. 2000. Function and mechanism of zinc metalloenzymes. *The Journal of nutrition*, **130**(suppl. 5S): 1437S–1446S. doi:10.1093/jn/130.5.1437S.

Itoh K, Chiba T, Takahashi S, Ishii T, Igarashi K, Katoh Y, Oyake T, Hayashi N, Satoh K, Hatayama I, Yamamoto M, Nabeshima Y. 1997. An nrf2/small maf heterodimer mediates the induction of phase II detoxifying enzyme genes through antioxidant response elements. *Biochemical and biophysical research communications*, **236** (2):313–322.

Kim S, Jung Y, Kim D, Koh H, Chung J. 2000. Extracellular zinc activates p70S6 kinase through the phosphatidylinositol 3-kinase signaling pathway. *The Journal of biological chemistry*, **275** (34): 25979-84. doi:10.1074/jbc.M001975200.

Kovala T, Sanwal BD, Ball EH. 1997. Recombinant expression of a Type IV, cAMP-specific phosphodiesterase: characterization and structure-function studies of deletion mutants. *Biochemistry* **36** (10): 2968-2976.

McMahon M, Swift SR, Hayes JD. 2018. Zinc-binding triggers a conformational-switch in the cullin-3 substrate adaptor protein KEAP1 that controls transcription factor NRF2. *Toxicology and applied pharmacology*, **360**: 45-57. doi:10.1016/j.taap.2018.09.033.

Vergnano AM, Rebola N, Savtchenko LP, Pinheiro PS, Casado M, Kieffer BL, Rusakov DA, Mülle C, Paoletti P. 2014. Zinc dynamics and action at excitatory synapses. *Neuron*, **82** (5): 1101-1114. doi:10.1016/j.neuron.2014.04.034.

Zago MP, Mackenzie GG, Adamo AM, Keen CL, Oteiza PI. 2005. Differential modulation of MAP kinases by zinc deficiency in IMR-32 cells: role of H2O2. *Antioxidants Redox Signal*, **7**:1773–1782.

MacDonald RS. 2000. The role of zinc in growth and cell proliferation. *The Journal of nutrition*, **130** 5S: 1500S-1508S.

Lo MN, Damon LJ, Tay JW, Jia Sh, Palmer AE. 2020. Single cell analysis reveals multiple requirements for zinc in the mammalian cell cycle. *eLife*, **9**: e51107, doi:10.7554/eLife.51107.

Omburo GA, Brickus T, Gazaleh FA, Colman RW. I 995. Divalent metal cation requirement and possible classification of cGMP-inhibited phosphodiesterase as a metallohydrolase. *Archives of Biochemistry and Biophysics*, **323** (1): 1-5.

Prasad AS. 1993. Historical Aspects of Zinc. In: *Biochemistry of Zinc Biochemistry of the Elements*. 11 Boston, MA: Springer. p. 1–15.

Supasai S, Aimo L, Adamo AM, Mackenzie GG, Oteiza PI. 2017. Zinc deficiency affects the STAT1/3 signaling pathways in part through redox-mediated mechanisms. *Redox Biology* **11**: 469–481. doi:10.1016/j.redox.2016.12.027.

Yamasaki S, Sakata-Sogawa K, Hasegawa A, Suzuki T, Kabu K, Sato E, Kurosaki T, Yamashita S, Tokunaga M, Nishida K, Hirano T. 2007. Zinc is a novel intracellular second messenger. *The Journal of Cell Biology*, **177**: 637–645.

Zhuo S, Dixon JE. 1997. Effects of sulfhydryl reagents on the activity of lambda Ser/Thr phosphoprotein phosphatase and inhibition of the enzyme by zinc ion. *Protein engineering*, **10 (12)**: 1445–52. doi:10.1093/protein/10.12.1445.

Samet JM, Graves LM, Quay J, Dailey LA, Devlin RB, Ghio AJ, Wu W, Bromberg PA, Reed W. 1998. Activation of MAPKs in human bronchial epithelial cells exposed to metals. *The American Journal of Physiology*. **275**: L551–8. PMID 9728050 DOI: 10.1152/Ajplung.1998.275.3.L551.

Sanford A. Palmer E. 2020. Dissociated hippocampal neurons exhibit distinct Zn²⁺ dynamic in a stimulation-method-dependent manner. *ACS chemical neuroscience*, **11 (4)**: 508–514. doi:10.1021/acscchemneuro.0c00006.

Seshacharyulu P, Pandey P, Datta K, Batra SK. 2013. Phosphatase: PP2A structural importance, regulation and its aberrant expression in cancer. *Cancer letters*, **335, (1)**: 9–18. doi:10.1016/j.canlet.2013.02.036.

Vallee BL, Falchuk KH. 1993. The biochemical basis of zinc physiology. *Physiological reviews*, **73 (1)**: 79–118. doi:10.1152/physrev.1993.73.1.79.

Maret W, Vallee BL. 1998. Thiolate ligands in metallothionein confer redox activity on zinc clusters. *Proceedings of the National Academy of Sciences of the United States of America*, **95 (7)**:3478–3482. doi: 10.1073/pnas.95.7.3478. PMID: 9520391; PMCID: PMC19861.

Wu W, Graves LM, Jaspers I, Devlin RB, Reed W, Samet JM. 1999. Activation of the EGF receptor signaling pathway in human airway epithelial cells exposed to metals. *The American journal of physiology*, **277 (5)**: L924–31. doi:10.1152/ajplung.1999.277.5.L924.

Ho Y, Samarasinghe R, Knoch ME, Lewis M, Aizenman E, DeFranco DB. 2008. Selective inhibition of mitogen-activated protein kinase phosphatases by zinc accounts for extracellular signal-regulated kinase 1/2-dependent oxidative neuronal cell death. *Molecular Pharmacology*, **74(4)**:1141–115. <https://doi.org/10.1124/mol.108.049064> PMID: 18635668 PMCID. PMC2575064

Qin Y, Dittmer PJ, Park JG, Jansen KB, Palmer AE. 2011. Measuring steady-state and dynamic endoplasmic reticulum and Golgi Zn²⁺ with genetically encoded sensors. *Proceedings of the National Academy of Sciences of the United States of America*, **108(18)**: 7351–7356. <https://doi.org/10.1073/pnas.1015686108>.

Yan M, Song Y, Wong CP, Hardin K, Ho E. 2008. Zinc deficiency alters DNA damage response genes in normal human prostate epithelial cells. *The Journal of Nutrition*, **138(4)**:667–673.