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RABBITS ARGINASE I AND II: ACTIVITY AND pH SENSITIVITY OF SELF-FORMATION POLYPEPTIDES

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Protein-protein interactions underlie supramolecular self-formation structures (including enzymes). Nowadays, they have a crucial role, as they contribute to the creation of biological substances with a certain function. Due to their unique properties, proteins, and enzymes have been widely studied in the last few years and their important roles in health and various diseases have been proven from this point of view, many enzymes are characterized by the process of self-formation ("self-assembly") depending on different conditions. Such an enzyme is arginase (including isoenzymes I and II), which can be considered as a biomarker clarifying the pathological conditions of the organism. Based on this, we aimed to create simple fractal models and study the changes in oligomeric structure (depending on pH and time) during the reversible inactivation of rabbit arginase I and II and elucidate the unique aspects of "self-assembly". We have shown that the "false" oligomers formed in the process of protein "self-assembly" *in vitro* can appear as intermediate structures endowed with enzymatic activity.

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Introduction. Most of the biological functions in the cell are carried out with the participation of enzymes or through their mediation. Enzymes often function as complex and highly ordered systems containing multiple polypeptide chains. For the formation of such systems, proteins must have specially arranged sections on their surface, ensuring a certain connection with other system components. There are several common ways to study the structural features of enzymes, including acid inactivation (denaturation) and subsequent reactivation (renaturation) of proteins, which in turn can disrupt the homeostasis of intracellular metabolism, leading to the development of metabolic diseases. All this is the basis for assuming that the "self-assembly" of the polypeptide chain is a directed process and takes place in stages [1]. It plays an important role in biological systems, as many cellular structures result from the self-assembly of proteins or lipids, such as intermediate filaments and vesicles [2]. A polypeptide chain in a protein cannot adopt all possible conformational

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states, because denatured proteins lack an ordered surface. Consequently, they cannot effectively communicate with other components of the system, as changes are made to the spatial structure of the protein. This process requires a specific period and optimal conditions (such as pH and temperature). Any change in an enzyme's properties can contribute to a conformational transition unless significant biochemical or structural changes occur. The preservation of the characteristic enzyme conformation is possible due to the formation of multiple weak bonds between individual segments of the polypeptide chain [3]. As a result of a slight change in the internal environment, a conformational change can be observed, even at the level of the III and IV structure, which significantly modifies the functions of the protein [4, 5]. Such changes can occur under the influence of various factors, starting from dilution of the solution to denaturing factors, changing the pH of the environment, and others. According to literature data, changes in pH can depend on the state of acidic and basic groups and the degree of ionization. A change in pH can influence the permeability of the cell membrane, thus changing the distribution of substances and ions on both sides of it. Metal ions and low-molecular organic compounds participate in that process too, but hydrophobic interactions and hydrogen bonds have a greater effect, their cumulative effect is often sufficient for forming a quaternary structure. All this contributes to the violation of the conformational stability of enzymes is the basis for the pathogenesis of many human diseases [6].

In contemporary biomaterial design, various innovative strategies incorporate self-assembled structures, leveraging supramolecular interactions as a key driving force. One such biomolecule of interest is the arginase enzyme, which exists in different isoforms, notably cytoplasmic arginase I (hepatic arginase) and mitochondrial arginase II. While primarily produced in the liver, arginase is also present in non-hepatic tissues, such as the kidney, brain, mammary gland, and prostate gland, where the complete ornithine cycle is absent. In these organs, arginase plays a role in the homeostasis of L-arginine and participates in the biosynthetic biotransformation process, including the synthesis of polyamines, glutamate, and proline, thereby regulating the L-ornithine metabolic pathway [7–9]. A common feature of all arginases thus far studied, whether of eukaryotic or prokaryotic origin, is a requirement of divalent cations for activity. Mn^{2+} is the physiologic activator, although the divalent cation requirement for some arginases has been reported to be satisfied by Co^{2+} and Ni^{2+} [10]. Based on the mentioned above, the study of this problem will allow the development of targeted measures and create simple fractal models that will regulate the biological processes of organisms [11–14].

The research will contribute to understanding the degree of instability and variability of the enzyme's conformation and the mechanisms of correction. Considering all this, the research work aims to study the changes in the activity of rabbit arginase I and II (kidney, brain) enzymes, which were subjected to deactivated (under acidic conditions) and reactivated (under basic conditions). The reactivation was performed with different ions, in different pH conditions, to evaluate the properties of self-assembled "pseudo-polypeptides". We considered the main facts of the research on the example of a model of reversible inactivation of type I and II arginase and carried out experimental work to evaluate the activity and pH optimum of the denatured enzyme and the self-assembled polypeptides formed in this process.

Materials and Methods.

Chemicals and Reagents. All chemicals and reagents were purchased from "Sigma-Aldrich GmbH" (Taufkirchen, Germany).

Animals. The experiments included 5 male rabbits (*Oryctolagus cuniculus* ssp. *domesticus*) with a mass of 800–1200 *g*. The animals maintained a 12 *h* light/12 *h* dark cycle at 18–23°C, for experimental research livers, kidneys, and brains of animals were used. The organs separated from the animals were carefully dried with filter paper, weighed, and subjected to homogenization in a Daihan – Homogenizer (Germany) at +4°C.

Ethical Approval. Animal research was approved by the National Center of Bioethics (Armenia) and according to regulations outlined in the 2010/63/EU (2010/63/EU, 2010) [15].

Arginase Activity. The modified Diacetyl Monoxime colorimetric method was employed to assess the arginase activity in tissue homogenate [15]. The intensity of the yellow color was measured spectrophotometrically at a wavelength of 487 *nm* (Genesys10, USA) [16].

Arginase Deactivation and Reactivation. Acid inactivation of the enzyme was carried out under the influence of 0.05 *M* glycine-HCl buffer (pH 4) at room temperature. The reactivation of inactivated arginase was carried out with 0.05 *M* glycine-NaOH buffer (pH 9.5) at +20°C, in the presence of Mn^{2+}, Ni^{2+}, and Co^{2+} chlorides (25 *μmol* in 1 *mL* of the test sample).

Statistical Analysis. The obtained results were presented as the mean values (*M* ±SD). Statistical analyses were performed using GraphPad Prism 8 software (San Diego, USA), and a significance level of $p < 0.05$ was deemed statistically significant.

Results.

The Change of the Activity of Arginase I (Liver) as a Result of the Reversible Inactivation of pH-Dependent "Self-Assembled" Polypeptides. Based on literature data and the aim of our work, in the first stage, the change of arginase I activity was evaluated depending on different pH conditions and hours. For this, first of all, the activity of arginase was evaluated under optimal conditions of pH 9.5. In the next stage, its reactivation was carried out under conditions of pH 4.5, followed by its reorganization with metals Mn^{2+} (a), Ni (b), and Co^{2+} (c) at pH 7.4, pH 8.6, pH 9.0, pH 9.5, pH 10.0. Moreover, at all pH values the activity of the reconstituted enzyme was evaluated in 24 *h*, 48 *h* and 72 *h*. The results showed that in the case of reactivation with Mn^{2+} (Fig. 1, a) at pH 7.4, a decrease in arginase activity was observed at 24 *h* and 48 *h* by 26% and 23%, respectively, compared to the control group. And in the 72nd *h*, the activity increased by about 3% compared to the control group. As for pH 8.6 and pH 9, in this case, almost the same picture was observed as in the conditions of pH 7.4. Under conditions of pH 9.5 and pH 10, compared to the control group, enzyme activity decreased by about 21–25% at 24 *h* and 48 *h*. In the 72nd *h* of the given pH, the activity of the enzyme increased by about 3–5%. In the case of reactivation with Ni^{2+} (Fig. 1, b), enzyme activity decreased by 53% at 24 *h* and 48 *h* compared to the control group at pH 7.4. At pH 8.6, the activity decreased by 43% and 55% at 24 *h* and 48 *h*, respectively. And at 72 *h*, activity increased by 18%. At pH 9, the activity decreased by about 50% at 24 *h* and 48 *h* and on the 72nd *h*, it increases by 10%. At pH 9.5 and pH 10.0, almost the same

picture was observed: at 24 *h* and 48 *h*, the activity decreased by 43–45%, and at 72 *h*, the activity increased by 8%.

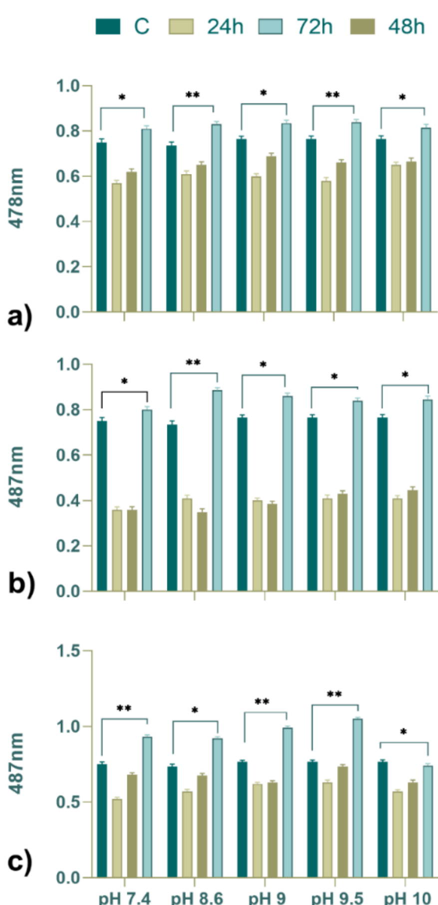

Fig. 1. The change of the activity of pH-dependent "self-assembled" polypeptides: a) Mn^{2+}; b) Ni^{2+}; c) Co^{2+} as a result of the reversible inactivation of mammalian arginase I (liver): $n = 5$; * – $p < 0.05$; ** – $p < 0.01$.

Reactivation with Co^{2+} (Fig. 1, c), the following results were obtained: enzyme activity decreased by 35% and 15% at 24 *h* and 48 *h*, respectively, compared to the control group at pH 7.4. At the same pH, activity increased by 18% at 72 *h*. At pH 8.6, the activity decreased by 28% and 15% at 24 *h* and 48 *h*, respectively, but at 72 *h*, activity increased by 15%. At pH 9.0, the activity decreased by about 21% at 24 *h* and 48 *h*. And in the 72nd *h*, it rose by 31%. At pH 9.5, there was a 21% decrease at 24 *h*, an 8% decrease at 48 *h*, and a 57% increase in activity at 72 *h*. At pH 10.0, activity decreased by 28% and 21% at 24 *h* and 48 *h*, respectively. The obtained results indicate that Co^{2+} polypeptide activity is higher at pH 9.5, although Mn^{2+} was the actual cofactor in the native enzyme cofactor.

The Change of the Activity of Arginase II (kidney) as a Result of the Reversible Inactivation of pH-Dependent "Self-Assembled" Polypeptides. The next phase of research was to evaluate the change of arginase II activity in both kidney and brain homogenates. For each experiment, has been selected a control with a suitable pH, with Mn^{2+} serving as a coenzyme (Fig. 2, a). In this case chosen same conditions, as mentioned above, such as hours 24 *h*, 48 *h*, and 72 *h*, and different pH values. The change of enzyme activity in kidney homogenate at 24 *h* at pH 7.4 was recorded as follows, enzyme activity decreased by about 54% at 24 *h*, 59% at 48 *h*, and 57% at 72 *h* compared to the control group. At pH 8.6, the change in activity relative to the control group decreased as follows, 63–66% at 24th and 48th *h*, and 49% at 72nd *h*. At pH 9, compared to the control group, the activity decreased by about 57% at 24 *h*, and at 48 *h* and 72 *h* almost the same rebound was observed with activity decreased by about 66%. The enzyme activity at 24 *h* at pH 9.5 decreased by about 66%, and at 48 *h* and 72 *h*, by 69% and 62%, respectively. In the case of pH 10.0, compared to the control group, the activity decreased by about 58% in the 24th *h*, by 60% in the 48th *h*, and by 65% in the 72nd *h*.

In the case of reactivation with Ni^{2+} (Fig. 2, b), the following changes were observed: at pH 7.4, compared to the control group, arginase activity decreased by 59% at the 24th *h*, by 64% at the 48th *h*, and by 40% at the 72nd *h*. At pH 8.6, enzyme

activity decreased at 24 *h*, 48 *h*, and 72 *h*, correspondingly by 59%, 67%, and 64%. At pH 9, the decrease in activity was recorded as follows: 65% at the 24th *h*, 71% at the 48th *h*, and 61% at the 72nd *h*. At pH 9.5, activity decreased by 64%, 75%, and 40% at 24 *h*, 48 *h*, and 72 *h*, respectively. At pH 10.0, arginase 2 activity decreased by about 68% at 24 *h* and 48 *h*, and by 41% at 72 *h*.

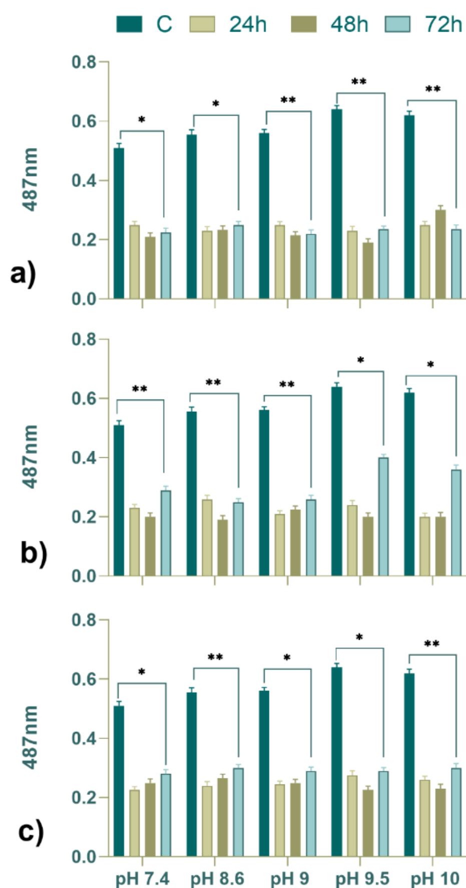

Fig. 2. The change of the activity of pH-dependent "self-assembled" polypeptides: a) Mn^{2+}; b)Ni^{2+}; c) Co^{2+} as a result of the reversible inactivation of mammalian arginase II: $n = 5$; * – $p < 0.05$; ** – $p < 0.01$.

As for the reactivation of the enzyme with Co^{2+} (Fig. 2, c), the activity of the enzyme was also decreased particularly in the case of pH 7.4, the activity decreased by about 62% at the 24th *h*, at the 48th *h* by 60%, and at 72nd *h* by 54%. In the case of pH 8.6 and pH 9,0, almost the same results were recorded, arginase activity at 24 *h*, 48 *h*, and 72 *h* decreased by 63%, 57%, and 50%, respectively. Change of arginase activity under pH 9.5 conditions was recorded as follows: 54% reduction at 24 *h*, 66% at 48 *h*, and approximately 51% at 72 *h*. At pH 10.0, a decrease in enzyme activity was also observed, by about 62%, 67%, and 53% at 24 *h*, 48 *h*, and 72 *h*, respectively.

The results of arginase II (kidney) studies showed that, unlike hepatic arginase reactivation, the activity of self-assembled Ni^{2+} polypeptide exceeded other versions (Mn^{2+} and Co^{2+}) at pH 9.5 at the 72nd *h* (Fig. 2, b).

The Change of the Activity of Arginase II (Brain) as a Result of the Reversible Inactivation of pH-Dependent "Self-Assembled" Polypeptides. The change in arginase II activity in brain homogenate is dramatically different from the change in arginase II activity in kidney homogenate. In this case, in the case of reactivation with Mn^{2+} (Fig. 3, a), compared to the control group, an increase in activity was observed at all pH values only at the 72nd *h*. The data showed that at pH 7.4, the enzyme activity decreased by about 29% at the 24th *h*, by 53% at the 48th *h*, and increased by about 3 times at the 72nd *h*. At pH 8.6, it decreased by about 41% at 24 *h* and 32% at 48 *h*. At hour 72, activity has increased by about 2.3 times. Enzyme activity at pH 9.0 decreased by 57% at 24 *h*, 50% at 48 *h*, and increased by about 2.5 times at 72 *h*. At pH 9.5, arginase activity decreased by about 69%, and by 73% at 48 *h*. At the 72nd *h*, it increased by about 1.2 times. In the case of pH 10, in the 24th and 48th *h*, the activity of the enzyme decreased

by 66% and 71%, respectively, and in the 72nd *h*, it increased by about 1.3 times. The results were obtained by comparing them to the control group of each group.

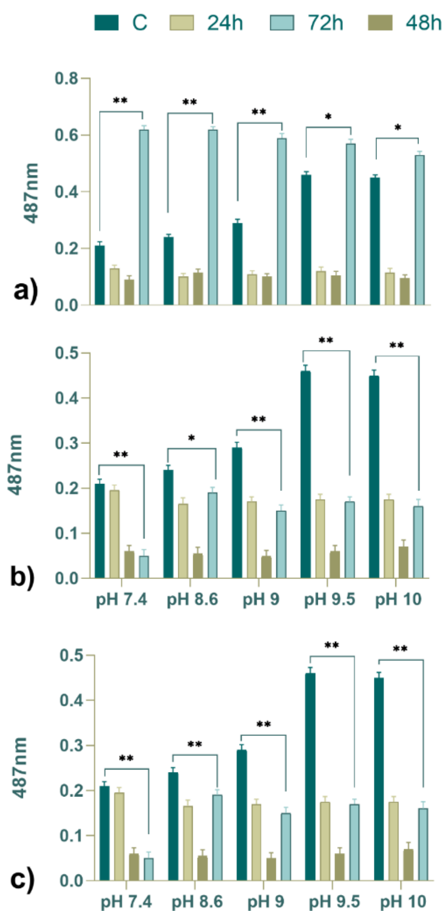

Fig. 3. Change in activity of pH-dependent "self-assembling" polypeptides: a) Mn^{2+}; b) Ni^{2+}; c) Co^{2+} as a result of reversible inactivation of mammalian arginase II (brain): $n = 5$; * – $p < 0.05$; ** – $p < 0.01$.

In the case of reactivation with nickel and cobalt metals, enzyme activity decreased at all pH values compared to the control group. In particular, reactivation with nickel (Fig. 3, b) at pH 7.4 enzyme activity decreased by 19% in the 24th *h*, by 78% in the 48th *h*, and by about 87% in the 72nd *h*. At pH 8.6, activity decreased by 30%, 84% and 25%, respectively, at the 24th, 48th and 72nd *h*. At pH 9, arginase activity decreased by about 33% at the 24th *h*, by 45% at the 48th *h*, and by about 60% at the 72nd *h*. At pH 9.5, enzyme activity decreased by about 60% at 24 *h*, by 88% at 48 *h*, and by 58% at 72 *h*. In the case of pH 10 at the 24th *h*, it decreased by about 58%, at 48 *h* by 84%, and at 72 *h* by about 60%.

The following results were obtained upon reactivation with Co^{2+} (Fig. 3, c). At pH 7.4, activity decreased by 18% at 24 *h*, 73% at 48 *h*, and 82% at 72 *h*. At pH 8.6, the following changes were observed, activity decreased by 34% at 24 *h*, 79% at 48 *h*, and 25% at 72 *h*. At pH 9.0, enzyme activity decreased by 43%, 88%, and 46% at 24 *h*, 48 *h*, and 72 *h*, respectively. At pH 9.5, enzyme activity decreased by 65% at 24 *h*, 86.5% at 48 *h*, and 65% at 72 *h*. At pH 10.0, enzyme activity decreased by 64%, 82%, and 66% at 24 *h*, 48 *h*, and 72 *h*, respectively.

The data obtained in the process of deactivation of brain arginase II showed that the activity of Mn^{2+} polypeptide was significantly increased at all pH values and higher than the baseline at the 72nd *h* (Fig. 3, a).

The results of the research work show that deactivation contributes to the change of spatial structure of the enzyme. Particularly, under the conditions used in this research work reactivation of the inactivated, enzyme made 40–70% at 24–72 *h*, under different pH values (7.4, 8.6, 9.0, 9.5, and 10.0). The reactivated polypeptides showed the highest catalytic activity in significantly different pH conditions such as (arginase I $Co^{2+}>Ni^{2+}>Mn^{2+}$, arginase II (kidney) $Ni^{2+}>Co^{2+}>Mn^{2+}$, arginase II (brain) $Mn^{2+}>Co^{2+}=Ni^{2+}$) depending on the degree of reactivation (Figs. 1–3).

At different pH values, the enzyme's active center can be in a partially ionized or non-ionized state, which is reflected in the III structure of the protein, activity, and enzyme-substrate subject. Analysis showed that liver-type arginase I is more

stable under acid inactivation conditions compared to arginase II (kidney, brain) [17]. The functional forms of arginase inactivated under acidic conditions (pH 4.0) were reactivated (pH 9.5) by the presence of Mn^{2+} (physiological cofactor) and Co^{2+}, Ni^{2+} cations, and "self-assembled" as a result of the inactivation of arginase I and II.

Discussion. Thus, enzymes adapt to stress conditions by increasing their instability, a property enabling them to effectively respond to various environmental factors. Changes in arginase stability, possibly induced by weakened bonds with its promoters or divalent ions, may represent a biologically targeted mechanism for regulating enzyme activity. Upon deactivation, arginase changes spatial structure and charge, affecting its activation degree under specific conditions and the process of oligomeric structure formation. Reactivated oligomers exhibit maximal catalytic activity under significantly different pH conditions.

At varying pH levels, the enzyme's active center can exist in a partially ionized or non-ionized state, impacting its protein structure (including its tertiary structure), activity, and enzyme-substrate interactions. Environmental shifts can induce conformational changes in enzymes, leading to activity loss, denaturation, or altered enzyme molecule charge.

Enzyme conformation, encompassing its primary, secondary, tertiary, and quaternary structure, plays a crucial role in the pathogenesis of various human diseases. Understanding enzyme structure stability can help elucidate pathogenesis in certain human diseases. Additionally, enzyme molecules possess structural features that can either facilitate or impede the formation of pathological conformations.

Our study, employing simple fractal models, sheds light on processes involved in protein self-assembly, enables estimation of enzyme self-assembly rates, and emphasizes the critical stage of self-assembly the formation of cores.

Conclusion. Summarizing the results of the work, it should be noted that in the protein "self-assembly" process *in vitro*, the formed *in vitro* "false" polypeptides can maintain enzymatic activity. Studies of the activity and pH sensitivity of mammalian arginase I and II, "self-assembling"'polypeptides, allow us to obtain information about the nature of the functional groups included in the composition of the active center of the enzyme, and their ionizing properties and characteristics of the cofactor connection. All of this can be used in biomedicine, to prevent different types of diseases

These results will serve as a basis for further. They will allow us to create new animal models that have different diseases, and elucidate the molecular mechanism of "self-assembly, due to the change of activity of diverse enzymes.

All authors contributed to the concept and design of the study. SH conducted the experiments and analyzed the results. The manuscript was written by SH, EB, and NA. EB and NA supervised the experiments, and corrected and edited the manuscript. All authors revised and accepted the final version of the manuscript.

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ՃԱԳԱՐԻ ԱՐԳԻՆԱԶ I ԵՎ II ՖԵՐՄԵՆՏՆԵՐԻ ԻՆՔՆԱԿԱԶՄԱԿԵՐՊՎԱԾ ՊՈԼԻՊԵՊՏԻԴՆԵՐԻ ԱԿՏԻՎՈՒԹՅՈՒՆԸ ԵՎ pH ԶԳԱՅՈՒՆՈՒԹՅՈՒՆԸ

Գերմոլեկուլային ինքնակազմակերպվող կառուցվածքների (ներառյալ ֆերմենտները) հիմքում ընկած են սպիտակուց-սպիտակուց փոխազդեցությունները: Մեր օրերում դրանք վճռորոշ դեր ունեն, քանի որ նպաստում են առանցքային ֆունկցիա ունեցող կենսաբանական նյութերի ստեղծմանը: Իրենց յուրահատուկ հատկությունների շնորհիվ սպիտակուցները և ֆերմենտները լայնորեն ուսումնասիրվել են վերջին մի քանի տարիներին և ապացուցվել է նրանց կարևոր դերը տարբեր հիվանդությունների ժամանակ: Այս տեսանկյունից կան բազմաթիվ ֆերմենտներ, որոնք բնութագրվում են տարբեր պայմաններից կախված ինքնահավաքման գործընթացով: Այդպիսի ֆերմենտներից է արգինազը (ներառյալ I և II իզոֆերմենտներ), որը կարող է դիտարկվել որպես օրգանիզմի պաթոլոգիական պայմանները պարզաբանող կենսամարկեր: Ելնելով այս ամենից՝ մենք նպատակ ունեինք ստեղծել պարզ ֆրակտալ մոդելներ և ուսումնասիրել օլիգոմերային կառուցվածքի փոփոխությունները՝ կախված pH-ից և ժամանակից ճագարի արգինազ I և II շրջելի ինակտիվացման ընթացքում և պարզաբանել «ինքնահավաքման» եզակի կողմերը: Արդյունքները ցույց են տվել, որ սպիտակուցի *in vitro* «ինքնահավաքման» գործընթացում առաջացած «կեղծ» օլիգոմերները կարող են ներկայանալ որպես միջանկյալ կառուցվածքներ՝ օժտված ֆերմենտային ակտիվությամբ:

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АКТИВНОСТЬ И pH-ЧУВСТВИТЕЛЬНОСТЬ САМОСБОРНЫХ ПОЛИПЕПТИДОВ КРОЛИЧЬЕЙ АРГИНАЗЫ I И II

Белково-белковые взаимодействия лежат в основе супрамолекулярных самоформирующихся структур (в том числе ферментов). В настоящее время выяснено, что им принадлежит решающая роль в создании биологических веществ с определенными функциями. В последние несколько лет уникальные свойства белков и ферментов широко изучались и была доказана их важная роль в различных заболеваниях. Так существует множество ферментов, для которых характерен процесс самоформирования (“самосборки”) в зависимости от разных условий. Одним из таких ферментов является аргиназа (в том числе изоферменты I и II), которую можно рассматривать как биомаркер, патологического состояния организма. Основываясь на этом, мы стремились создать простые фрактальные модели и изучить изменения структуры олигомеров (в зависимости от pH и времени) при обратимой инактивации кроличьей аргиназы I и II, а также выяснить уникальные аспекты ее “самосборки”. Нами показано, что “ложные” олигомеры, образующиеся в процессе “самосборки” белков *in vitro*, могут представлять собой промежуточные структуры, наделенные ферментативной активностью.