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A link between β-catenin and hypertrophy: evaluation and meta-analysis

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Heart is a terminally differentiated organ almost unable to regenerate. The remodeling and hypertrophic growth are believed to be the main mechanisms of heart renovation after workloads or injury. Although there have been major advances in the identification of the genes and signaling pathways involved in mediating hypertrophy, further characterization of the underlying molecular mechanisms is needed due to the overall complexity of this process. **Aim.** The present work is an attempt to systematically assess the previous research on a β-catenin role in the heart muscle hypertrophy development. We hypothesized that β-catenin is a member of universal and conserved regulatory pathway for different tissues and species. To test this hypothesis, we performed the meta-analysis of experimental data available in different databases. **Methods.** The literature data were analyzed via Origin 8.0 using the simple regression and two-way ANOVA methods. **Results.** The results allowed selecting the most reproducible hypertrophy markers which were appropriate for the study of β-catenin function in the hypertrophy response (SERCA, actin DIF, Axin-2, c-myc, CD1, BNP, ANP and total protein/DNA index). The analysis shows that a decrease in the β-catenin expression has an ambiguous effect on heart hypertrophy. **Conclusion.** We have drawn interesting conclusions on the model and species-specific link between the β-catenin level and hypertrophy development, as well as between some hypertrophic markers and β-catenin expression on one hand, and hypertrophy development *etc*. on the other hand. The results also allowed selecting the most reproducible hypertrophy markers.

Keywords: β-catenin, hypertrophy, heart, meta-analysis, linear regression

Introduction

Heart disease is a number one cause of death worldwide with the amount of people diagnosed constantly increasing due to the ageing of population and increased rates of obesity and diabetes, posing a significant healthcare burden [1]. According to the report of the European Heart Network and European Society of Cardiology in 2012, cardiovascular diseases cause more than 4 million deaths every year, 1.9 million of these are in the EU countries alone. These diseases are the cause of not only demographic problems and decrease in the quality of life but also have profound economic impact as EU economy alone looses €196 billion per year due to this reason.

The adult heart is a dynamic organ formed mainly by terminally differentiated cells (cardiomyocytes) that are unable to divide. The remodeling and hypertrophic growth are believed to be the main mechanisms of heart renovation after the overwork or injury. These mechanisms cause pathologic a pathologic remodeling response through the activation of intracellular signaling pathways and transcriptional mediators in cardiac myocytes [1]. The activation of these molecular pathways may initially augment cardiac output (adaptive hypertrophy). However, prolonged hypertrophy (pathological or maladaptive hypertrophy) leads to the heart failure and sudden cardiac death (SCD). Whilst there have been major advances in the identification of genes and signaling

pathways involved in mediating hypertrophy, it is clear that due to the overall complexity of hypertrophic remodeling further characterization of the underlying molecular mechanisms is needed. One such signaling pathway that plays a major role in both heart development and normal heart homeostasis is the Wnt/β-catenin pathway [2,3].

The Wnt signaling pathway is not only critical for the embryos heart formation and development but also seems to have beneficial effect on cardiac remodeling. A number of experimental works emphasize the critical importance of β-catenin in the development of hypertrophic response [4–6]. According to Qu and coauthors, [7] the cardiac-specific haploinsufficiency of β-catenin attenuates pressure-overload–induced cardiac hypertrophy after transverse aortic constriction (TAC) [1,8], while overexpression of a constitutively active form of β-catenin results in the dilated cardiomyopathy [9]. The importance of β-catenin-dependent signaling for the development of cardiac hypertrophy has also been confirmed *in vivo* on mice with conditional cardiac-specific knockout of β-catenin [10]. Unfortunately, the results demonstrated are controversial and suggest opposite function for β-catenin in the hypertrophy development. Thus, Baurand and coauthors have reported that β-catenin downregulation is necessary for adaptive cardiac remodeling and cardiac hypertrophy development [11]. Furthermore, several studies suggest that cardiac remodeling is improved in mice with the overexpression of Wnt signaling inhibitors such as the soluble Frizzled-related proteins [12]. Interestingly, cardiac-specific deletion of both gamma-catenin and β-catenin in adult heart leads to cardiomyopathy resulting in SCD [8].

The possible reason of such a controversial hypothesis may be the overall complexity of the Wnt signaling pathway itself [13]. But also the model used has the impact on the output of any research, as well as the factors taken into account, the methods used for the analysis *etc.* There is a number of genes believed to be directly or indirectly regulated by the Wnt/β-catenin signaling, namely, the hypertrophic genes (beta- and alfa-MHC (embryonic and adult myosin heavy chain, respectively), ANP (atrial natriuretic peptide), BNP (B-type of natriuretic peptide), SERCA (sarcoplasmic reticulum Ca2+-ATPase), different types of actin (actin DIF)), canonical Wnt pathway members genes (Axin-2, GSK3 (Glycogen synthase kinase 3)) and Wnt target genes (connexin-40 (Cx-40), c-fos, c-myc, cyclinD1 (CD-1) *etc)*. Different authors publish only some of them while others use the full panel. Also the researchers use different model organisms and/or lines/types (human, mouse, rat, rabbit, fish, chick, cat, *etc;* cell lines of primary cell cultures). There is the set of parameters that allows to detect the hypertrophy of the cells or organs (heart weight/body weight (HW/BW) and heart weight/tibia length (HW/TL) indexes, cell surface, cell width, protein/DNA level *etc)*. Thus to clarify the signaling function of b-catenin in hypertrophic tissue remodeling for the aims of the present work we focused on meta-analysis of available experimental papers with diverse experimental models and conditions. According to literature data b-catenin is known to be a member of universal and conserved regulatory pathway for different tissues and species. So we hypothesized that b-catenin is an important player in hypertrophic tissue remodeling and has significant positive effects across species and tissues of markers related to Wnt signaling pathway as a response to hypertrophy development. To test this hypothesis were performed the basic science experimental articles meta-analysis.

Materials and Methods

Search strategy and selection criteria

In June 2015 we carried out comprehensive literature searches in the PubMed, Medline and Google Scholar databases with no limit set for date of publication, using the following keywords: Wnt AND hypertrophy, heart AND hypertrophy. The language was limited to English. A total of 215 articles were identified with the initial search. The inclusion criteria for study selection were: 1) The articles in which the canonical Wnt signaling and hypertrophy markers and/or morphological criteria were analyzed;

2) The articles in which the association between β-catenin signaling activity and hypertrophy were evaluated; 3) The articles where the expression of β-catenin at different levels under tissue remodeling was analyzed. The exclusion criteria were: 1) Articles without authors' original research data; 2) Articles without numeric data, hypertrophy markers mentioned *etc.* (Fig. 1). The search identified 100 articles which were eligible for quantitative analysis in this meta-analysis. The majority (97) of selected studies consisted of the laboratory experiments, and 5 were the laboratory studies of samples of patient tissues (Supplement 1). The detailed information of 100 relevant citations is listed in Supplement 1, too.

Data extraction and study assessment

Two researchers (OLP and LLM) independently extracted data and reviewed the essence of the articles to determine whether or not they met the criteria for inclusion. All disagreements were discussed (OOP and OLP). The data extract form was developed accordingly. One of the mentioned authors (OLP) extracted the following data from the included studies: species, tissue, hypertrophy level and approach to hypertrophy level assessment, and, if any: β-catenin expression level, protein/DNA ratio, and expression of genes: GSK3b, CD1, ANP, BNP, b-MHC, a-MHC, SERCA, Axin-2, different types of actin (actin DIF), cadherin, connexin-43 (Cx43), c-myc, TCF/Lef (T-cell factor/lymphoid enhancer factor), c-fos, VEGFR (Vascular Endothelial Growth Factor Receptor), LRP (low-density lipoprotein), SFRP4 (secreted frizzled-related protein 4), TGFb (Transforming Growth Factor-b), mTOR (mammalian target of rapamycine), authors, year of publication. The other author (LLM) checked the extracted data, and their disagreements were resolved in the discussion with other two authors (OOP and OLP) for all issues.

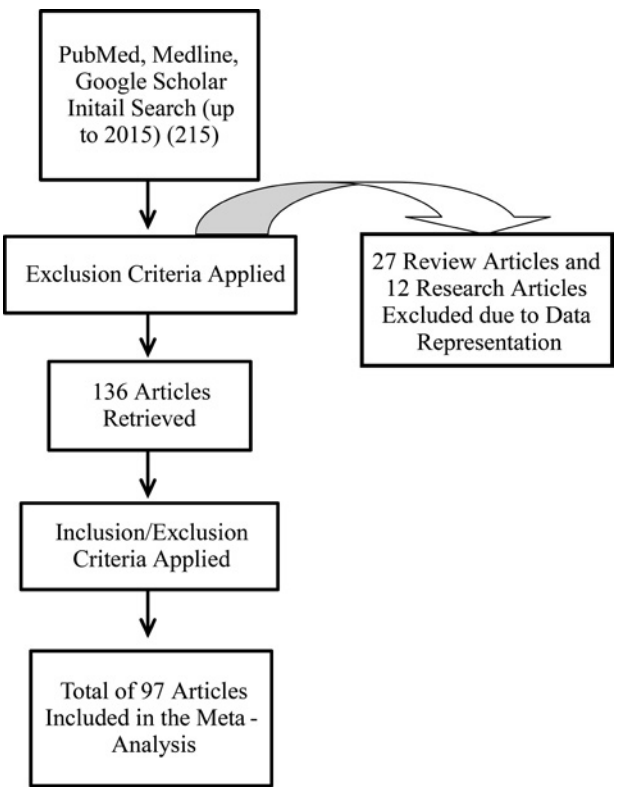

Fig. 1. The PRISMA flow diagram.

Statistical analysis

The Aggregate Data approach was used. Primarily, the Pearson correlation coefficient was calculated using the standard procedures. Then one-way ANOVA for tissue- and specie-specifity, and for data obtained in heart tissue of rodents was performed. For statistical analysis of the received data the simple regression method was used.

For the reason there were no clinical trials data among publication analyzed, and all experimental groups in these studies were small, we didn't administer data weighting.

For the factors which have no direct influence on each other two-way ANOVA (analysis of variance) was also applied.

Effect size was calculated by Hedges and Olkin.

Both publications – the one that demonstrated and the one that didn’t, significant effect were included in the analysis; the fail-safe number was calculated by Rosenthal method.

All calculations were performed with Origin 8.1.

Results and Discussion

The usage of appropriate criteria for heart hypertrophy evaluation is one of the most crucial points in

basic and medical research. That is why we began our work with an analysis of the correlation of the most common indices and criteria. For morphological analysis of heart hypertrophy some scientists use HW/TL index, and some other – HW/BW index, respectively. These indices have been studied in correlation with cytological parameters of heart tissue under the hypertrophy (Supplement 1). We discovered statistically significant correlation ($p \leq 0.05$) between heart hypertrophy and HW/TL index (0.97), but not between heart hypertrophy and HW/BW index. It can be an indication of the fact that HW/TL index is more appropriate for heart hypertrophy evaluation.

As we mentioned above, the signaling function of β-catenin in hypertrophy development is quite controversial and one of our aims was to analyze the possible link between hypertrophy and β-catenin expression in different animal models. Using two-way ANOVA we found the significant influence of the β-catenin expression level on all used hypertrophy indices ($\eta^2=0.30$). Effect size and fail-safe number also have been calculated ($g=0.64$, $N_{fs}>103$ when $N_0=71$). No species specificity was observed (Fig. 2). These results supported the hypothesis about important role of β-catenin in hypertrophy response and do not contradict the idea about universal character of β-catenin involvement in the mechanism of hypertrophy in vertebrates (Fig. 2) [8,14,15].

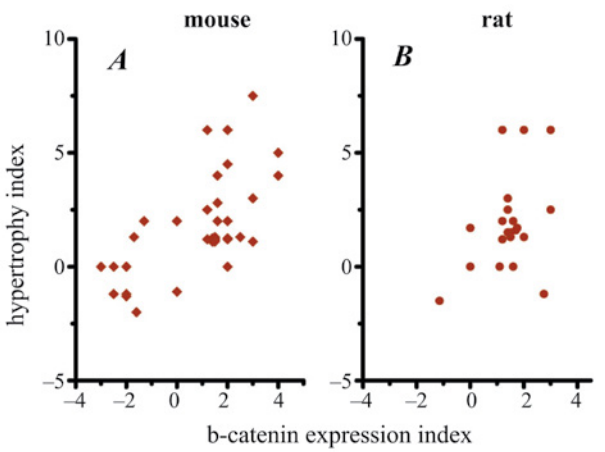

Fig. 2. B-catenin expression levels and hypertrophy indexes in mice (*A*) and rat (*B*).

The tissue specificity of correlation between the β-catenin expression level and hypertrophy index was found using two-way ANOVA ($\eta^2=0.25$, $g=0.59$, $N_0=62$, $N_{fs}>33$). In particular, in heart tissue decreasing in the β-catenin expression level leads both to hypertrophy induction and attenuation in other experimental works [12]. On the other hand, β-catenin expression induction always leads to hypertrophy response in heart. For deeper understanding of β-catenin function in heart hypertrophy we also analyzed the experimental works with cardiomyocytes and heart tissue. Using two-way ANOVA we revealed the significant influence of c-myc expression level on heart hypertrophy ($\eta^2=0.39$) and significant interaction between c-myc and β-catenin expression levels regarding it ($\eta^2=0.38$). These findings supports the idea about β-catenin involvement in heart hypertrophy via its signaling function as c-myc is one of known β-catenin target genes [16]. Also we found the significant interaction between ANP and β-catenin expression levels and in respect to hypertrophic remodeling ($\eta^2=0.095$) (Fig. 3). The effect size was $g=0.096$, $g=0.095$ and $g=0.17$, respectively, and in all of these cases the fail-safe number was insugnificant (<1). The first reason for this is the small number of papers describing hypertrophy markers, beta-catenin expression level, and ANP or c-myc expression ($N_0=12$ and 10, respectively). But another difficulty is much more meaningful, meaning the small sample size in each paper: the number of animals in control and experimental groups was within 2 and 10. Such a small sample size is not typical for clinical and psychological studies for which the meta-analysis approaches are mainly applied. But, the papers used for our analysis were focused mainly on the animal studies. The common practice in such a type of studies is to take much smaller sample size than it is in the human studies due to strict experiment conditions and lower heterogeneity in animal breeds comparing to human populations. Thus, despite analysis problems mentioned above, we still believe the results obtained are worthy.

In our analysis we showed the correlation between hypertrophy indices and the expression levels of some hypertrophy gene. Thus, we found the Pearson correlation between hypertrophy and SERCA ($r=0.87$, $p\leq0.05$) and hypertrophy and actin DIF ($r=0.71$, $p\leq0.05$) (Fig. 4).

Interestingly, we also found out the link between β-catenin and Axin-2 ($r=0.83$, $p\leq0.05$) in all works analyzed (Fig. 5).

The other parameter found to be reproducible was a total protein/DNA index. The strong link between this index and both hypertrophy ($r=0.83$, $p\leq0.05$) and β-catenin expression ($r=0.83$, $p\leq0.05$) was recovered.

Besides the results of the analysis described above we revealed not significant but close to statistical

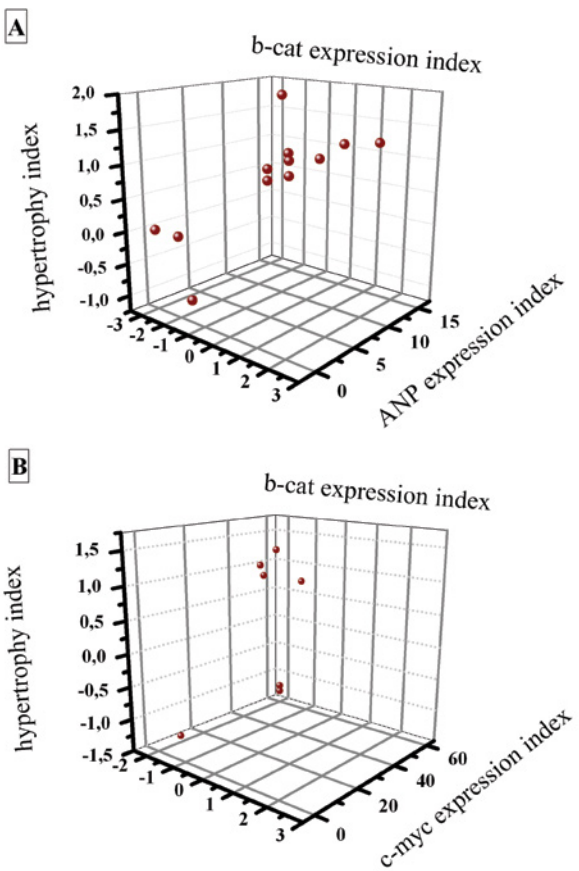

Fig. 3. ANP (A) and c-myc (B) expression levels, hypertrophy indexes and b-catenin levels.

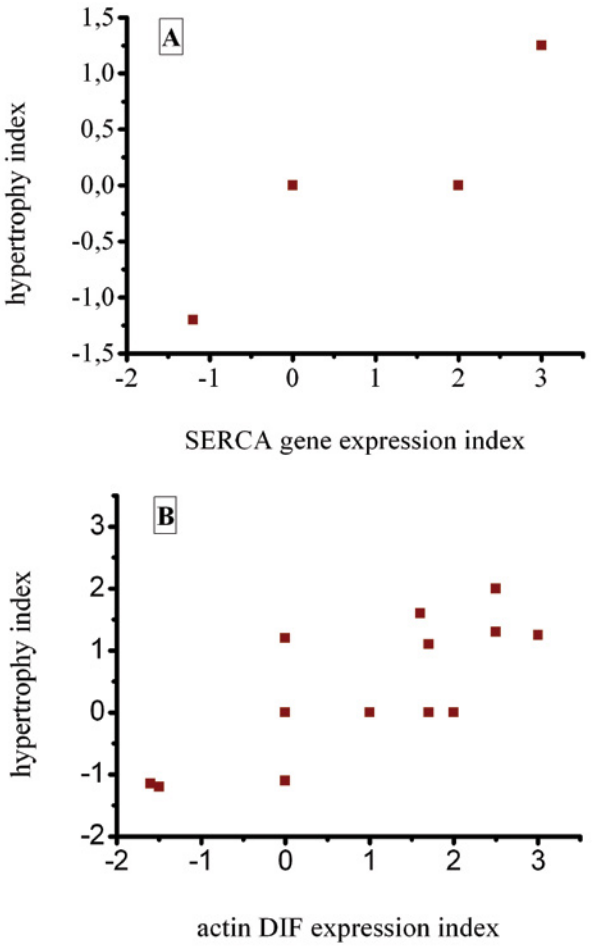

Fig. 4. SERCA (A) and actin DIF (B) expression levels and hypertrophy indexes.

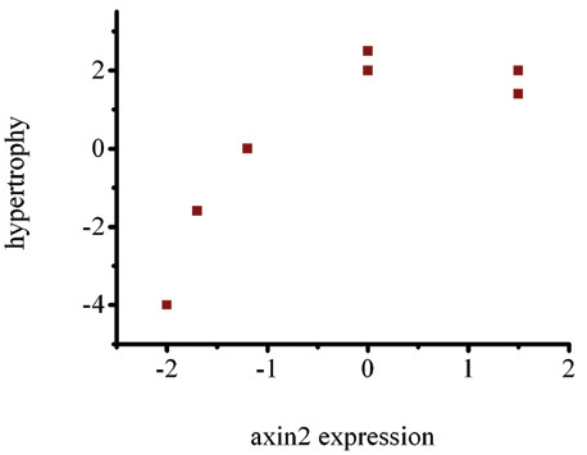

Fig. 5. Axin-2 expression level and hypertrophy indexes.

significance tendency for link between levels of expression of β-catenin and BNP ($p = 0.074$) and between hypertrophy indices and CD1 expression level ($p = 0.078$) in all tissues.

Our findings showed common fundamental mechanisms of hypertrophy responses in different experimental models. In our present analysis we supported the important role of β-catenin in hypertrophy response for all species used as model organisms. It is notable that, our analysis revealed the tissue-specific manner of interlink between the β-catenin expression level and hypertrophic response specifically in heart. The induction of β-catenin expression is clearly linked with heart hypertrophy response; these findings are in line with the experimental works [13,17–19] which demonstrated that β-catenin expression increasing is obligatory for the heart hypertrophy development. On the other hand, our analysis shows that decreasing in the β-catenin expression has ambiguous effect on heart hypertrophy. This result gave us the idea that role of β-catenin in heart hypertrophy is more complicated. It may depend on other signaling mechanisms and factors in heart [19,20]. Also we would like to note these findings may explain the experimental data [1] showing the necessity of β-catenin expression downregulation for hypertrophy development.

The results of our analysis allowed us to select the most reproducible hypertrophy markers which are appropriate for β-catenin function study in hypertrophy response, namely SERCA, actin DIF, Axin-2, c-myc, CD1, BNP, ANP and total protein/DNA index. It's important to note that some of these genes are already being used in clinics as markers for hypertrophy our opinion using the markers mentioned above may help to recover the β-catenin involvement in hypertrophy, especially in heart.

Conclusion

Summarizing, we would like to note that β-catenin is involved in hypertrophic response in a tissue-specific and multifarious manner. A wider and more detailed analysis of the β-catenin function in the hypertrophy regulation and its interlink with other signaling pathways is quite important. This knowledge might give a deeper insight in the hypertrophy mechanisms, and will be useful for therapeutical approaches.

Disclosure statement

The authors have no conflict of interests.

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Зв'язок між β-катеніном та гапертрофією: оцінка та мета-аналіз

О. Л. Пальчевська, Л. Л. Мацевич, О. О. Півень

Серце – прийнято вважати термінально диференційованих органом, який майже не регенерує. Перебудови міокарда і гіпертрофічний зростання є основними механізмами відновлення функції серця після надмірних навантажень і пошкоджень. В останні десятиліття багато робіт було присвячено ідентифікації генів і сигнально-регуляторних шляхів, залучених до вишеозначенние процесыв, але через складність останніх досліджження молекулярних механізмів, що лежать в основі розвитку гіпертрофії, не втрачає своєї актуальності. **Мета.** Дана робота є спробою систематично оцінити у вигляді мета-аналізу сучасні дослідженя, які стосуються ролі білка β-катеніна в розвитку гіпертрофії міокарда. **Методи.** Літературні дані, проаналізовано Origin 8.0 за допомогою методів простої регресії і two-way ANOVA. **Результати.** Відібрано маркери (SERCA, actin DIF, Axin-2, c-myc, CD1, BNP, ANP, а також індекс співвідношення вмісту білка і ДНК), що відтворюються в різних експериментальних умовах, які можуть бути використані для дослідження ролі β-катеніна в формуванні гипертрофического відповіді міокарда. Показано, що зниження рівня експресії β-катеніна має неоднозначний ефект на розвиток гіпертрофії міокарда. **Висновки.** Результати аналізу дозволяють зробити висновки про вплив експериментальної моделі на результати дослідження рівня експресії β-катеніна і його внесок в розвиток гіпертрофії, а також на існування такого зв'язку між деякими гіпертрофічна маркерами і рівнем експресії β-катеніна з одного боку і розвитком гіпертрофії – з іншого. Також встановлено, які з гипертрофических маркерів є найбільш відтвореними при різних умовах розвитку гіпертрофії.

Ключові слова: β-катенін, гіпертрофія, серце, мета-аналіз, лінійна регресія

Связь β-катенина и гипертрофии: эвалюация и мета-анализ

О. Л. Пальчевская, Л. Л. Мацевич, О. А. Пивень

Сердце – принято считать терминально дифференцированным органом, который почти не регенерирует. Перестройки миокарда и гипертрофический рост являются основными механизмами восстановления функции сердца после чрезмерных напряжений и повреждений. В последние десятилетия много работ было посвящено идентификации генов и сигнально-регуляторных путей, вовлеченных в вышеобозначенные процессы, но из-за сложности последних исследование молекулярных механизмов, лежащих в основе развития гипертрофии, не теряет своей актуальности. **Цель.** Данная робота является по-

пыткой систематически оценить в виде мета-анализа исследований, доступных в современной литературе, которые относятся к установлению роли белка β-катенина в развитии гипертрофии миокарда. **Методы.** Литературные данные, были проанализированы Origin 8.0 с помощью методов простой регрессии и two-way ANOVA. **Результаты.** Отобраны маркеры (SERCA, actin DIF, Axin-2, c-myc, CD1, BNP, ANP, а также индекс соотношения содержания белка и ДНК), воспроизводимые в разных экспериментальных условиях, которые могут быть использованы для исследования роли β-катенина в формировании гипертрофического ответа миокарда. Показано, что снижение уровня экспрессии β-катенина имеет неоднозначный эффект на развитие гипертрофии миокарда. **Выводы.** Результаты анализа позволяют сделать выводы о влиянии экспериментальной модели на результаты исследования уровня экспрессии β-катенина и его вкладе в развитие гипертрофии, а также на существование такой связи между некоторыми гипертрофическими маркерами и уровнем экспрессии β-катенина с одной стороны и развитием гипертрофии – с другой. Также установлено, какие из гипертрофических маркеров являются наиболее воспроизводимыми при разных условиях развития гипертрофии.

Ключевые слова: β-катенин, гипертрофия, сердце, мета-анализ, линейная регрессия

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