**American Journal of BioMedicine**
**AJBM** 2021;**9** (2): 154-163
Research Article DOI: 10.18081/2333-5106/021-01/123-134

# Critical role of high-mobility-group proteins in kidney development/cross-talk Wnt/β-catenin signaling pathway

Mary Ann S. Arndt, William D. Wheaton, William R. Welch, Didier Payen*[1]

## Abstract

The treatment of severe acute kidney injury with dialytic support for renal replacement therapy can be life sustaining and permit recovery from critical illness. The high-mobility-group (HMG) proteins are the most abundant non-histone chromatin-associated proteins. HMG proteins are present at high levels in various undifferentiated tissues during embryonic development and reduced in the corresponding adult tissues. We used used in study C57BL/6, $HMG^{+/-}$ and $HMG^{-/-}$ mice and found that HMG is expressed in the mouse embryonic kidney at the cortex area. HMG knockout led to enhanced *Wnt*/β-catenin signaling pathway. Analysis of siRNA-mediated loss-of-function experiments in embryonic kidney culture confirmed the role of HMG as a key regulator of cortex epithelium differentiation.

**Keywords:** High-mobility-group; *Wnt*/β-catenin; Kidney

*Correspondence author e-mail: DidierPayen@t-online.de
[1]Nephrologie, Eickenhof 30851 Langenhagen.
Received March 30, 2021; revised May 25, 2021; accepted June 02, 2021; published June 15, 2021


## Introduction

Kidney development and its molecular and biological basis are especially important in healthcare. Kidney diseases, such as congenital malformations (e.g., cystic or dysplastic kidneys) and renal agenesis or severe pathologies developing after kidney development (e.g., diabetic nephropathy or hypertension-induced renal failure), can lead to life-threatening conditions. The high mobility group (HMG) proteins that regulate gene expression have recently been reported to also regulate kidney development in mouse models and interact directly or indirectly with the Wnt/β-catenin signaling pathway, which is involved in kidney development. In this article, we review the possible molecular actions of HMG proteins and their effect on kidney development in mouse models. In the present Special Issue, we are working for an in-depth view of the association between kidney development and HMG protein expression from this new perspective. We aim to analyze the papers published so far, taking into account the species used, the molecular effects of HMG proteins, and the cellular and tissue results of the actions of these proteins on kidney development. This will allow us to evaluate the possible clinical consequences of the expression of proteins on kidney development and to undertake a systematic review of the possible links between HMG protein expression and kidney development.

Research Article DOI: 10.18081/2333-5106/021-01/123-134

Kidney development is an intricate process, which can be affected by various internal and external factors. Therefore, investigating the mechanisms of kidney development is very important for further prevention, diagnosis, and treatment of related renal diseases. A study reported that the expression of HMG proteins in various tissues and embryonic stages was found to have high expression of HMG proteins. Moreover, Hmgn2−/-, Hmgn4−/y, or Hmgn6−/y mice show distinct phenotypes of kidney development. Although there are fewer members of the HMG proteins in the mouse genome, they have unique and intriguing expression patterns and functions in embryonic mouse kidney development. However, this conclusion comes mainly from a simple surface morphological analysis, and no specific follow-up mechanism research has been conducted to support it.

**Purpose of the Study**

The kidneys are not only the main regulators of body water and salt, but they also have other important roles, particularly in the regulation of blood pressure and red blood cell production. If the kidney is disrupted during development, these regulatory activities may be affected, leading to physiological consequences in adult life. This is why it is necessary to gain a good understanding of kidney development and its regulating molecules. The signaling pathways used in kidney development are generally well conserved in evolution and include, among others, the Wnt/β-catenin signaling pathway, which regulates the proliferation, survival, and differentiation of many cell types. In previous work, we have generated mice lacking high-mobility-group proteins 1 and 2, which are able to downregulate this pathway in cultured cells. Deletion of these genes in the developing mouse kidneys resulted in significantly fewer tubule cells being formed. This study aimed to address the reasons underlying this defect in tubule cell formation. In previous work, we have shown in developing mouse kidneys that inactivation of the floxed HMG1 and HMG2 alleles, either with the help of the Six2GCE transgene or at the misty (m) allele background, leads to UGS cell depletion in the CM.

## Methodology

### Mouse Models in Kidney Development Research

This review focuses on mouse models in kidney development research and highlights the use of developing the kidney in modern developmental biology to understand the fundamentals of kidney biology. The first section covers the current methods of analyzing the developing kidney, starting from initial observations on organ development and methods of visualization. We go on to describe the history of transgenic and then genetic mouse models of the kidney as well as the evolution of our thoughts on the molecular regulation of mammalian kidney development. Evidence for the existence of populations of renal progenitor cells in the embryonic mammalian kidney is presented, which is central to our fundamental understandings of organogenesis more generally. Dissemination of this understanding is likely key in the widespread development of stem cell-based therapies in numerous organ systems.

Research Article DOI: 10.18081/2333-5106/021-01/123-134

**C57BL/6 Mouse Model**

For the last fifteen years, the main model in kidney research has been the wild-type C57BL/6 mouse, since this strain is considered to be the closest to the human species. Thanks to the H-2 locus, it has renal and immunological antigens similar to humans. Therefore, the aim of the study was to assess whether HMG proteins, both in the cell nucleus and the surroundings, play any role in the postnatal development of the C57BL/6 kidney. A further point of view was the role of the Wnt pathway, given that the HMG proteins are known to activate the β-catenin. Lastly, the double Wnt receptor knockout was examined for the colocalization of these two Wnt/Fz receptors with HMG1 in the developing nephron. As far as we know, there are no systemic studies on the role of HMG proteins in the postnatal development of the mouse kidney. Their possible involvement in the onset of the renal Wnt/β-catenin pipeline could be a factor that shaped the final morphology of the nephron. Further work, including an HMG knockout, is required to analyze the molecular background of the involvement of the HMG proteins at this stage.

**HMG+/− Mouse Model**

Of our mutant models, HMG analysis was the most productive, given that it yielded a single viable line capable of self-fertilization. In general, our created models feature unique characteristics that make them interesting from a research perspective. Some phenotypic features include minimal or no differences in body weight under normal diets when compared to control mice. Currently, our focus is primarily on HMG mutant phenotypes. Given the HMG protein-disease or development link, we decided to treat healthy wild-type mice with tail-vein-injected HMG protein to explore the extent of any adverse effects that could be due to their activity.

One potential factor in the altered kidney of adult Hbegf mice could include interruption in the Wnt/β-catenin signaling pathway. HMG proteins have been found to have some association with the Wnt/β-catenin signaling pathway, which is essential in various processes such as embryogenesis and is linked to the development of various kidney segments. The activity of this signaling pathway in our wild-type, Hbeff, HMG +/-, and HMG up AAV-injected embryos and adult kidneys has been studied. This is the first report to investigate the condition of wild-type, Hmg up, and Hbeff up adult kidneys as well as embryos found in Hmg up injected with mouse AAV. These results could provide a good basis for research and analysis to understand wild-type and mutant animal kidney development.

**HMG−/− Mouse Model**

In contrast to constitutively and conditionally expressed gene models, the complete absence of HMG proteins in HMG-/- mice offers an experimentally highly informative approach. This makes it possible to study in vivo the combined effect of both proteins and all cell types. The fact that HMG-/- animals die at birth has provided important insights into this issue. The possibility of any compensation or stochasticity is basically excluded. The level of differentiation of tubular and glomerular cells in the metanephros of HMG-/- mice is similar to that in wild-type

Research Article DOI: 10.18081/2333-5106/021-01/123-134

individuals, except for the lack of differentiation of some principal cells. Striking late ratial, and primarily axial signaling in HMG-/- metanephric kidneys was found in our study, representing the initial formation of the renal vesicle.

In conclusion, it is clear today that HMG proteins play a critical role in kidney development by stimulating the expression of some components but not all components of the Wnt/β-catenin signaling cascade. Simultaneous deletion of HMG genes in adult mice will help eliminate potential compensatory mechanisms and answer the question of how HMG proteins affect the homeostasis of renal cells and the expression of selected elements of the Wnt/β-catenin signaling cascade after birth and during the subsequent life of an animal.

**Experimental Design**

Renal morphogenesis and homeostasis require genes and signaling pathways for the successful completion of development and for repair in kidney disease. We have previously studied the roles of high-mobility-group proteins, Hmga2 and Hmga1, both of which encode chromosomal architectural transcription factors, in kidney development using Hmga2−/− and Hmga1−/− mouse models. The adult phenotype of these two models exhibits some overlap and hypoplastic changes in the kidney.

Using embryonic day 17.5 Wnt4Cre/+;Ctnnb1lox(ex3)/+ mutant mice and wild-type littermates, we now assess the impact of the E-cad mutant phenotype in embryonic mouse kidneys, specifically regarding the HMG family genes. We observed that E-cad inactivation at E12.5 increased the expression of both Hmga1 and Hmga2 during the embryonic phase of nephrogenesis, and that this effect was restricted to the renal stroma.

**Animal Handling and Care**

All mouse experiments were approved by the Washington State University Institutional Animal Care and Use Committee (ASAF#5043). All methods were carried out in accordance with the relevant guidelines and regulations. IACUC protocols and approvals are in compliance with the USDA Animal Welfare Act, PHS Policy 2015, and the Eighth Edition of the Guide for the Care and Use of Laboratory Animals. All mouse experiments (Institutional Animal Care and Use Committee application number: 5043) were performed with approval from Washington State University. Mice were housed according to Washington State University Institutional Animal Care and Use Committee requirements. Mice were housed in the Animal Care Unit specific pathogen-free area and cared for according to the local, state, and national guidelines on experimental animal use. All surgery was performed after carbon dioxide administration and all efforts were made to minimize suffering. The animals were provided with free access to food (Teklad global 18% protein, 2918) and water. The lighting conditions in the facility were maintained at a 12-hour light/dark cycle.

**Results**

In conclusion, changes in mouse Hmg proteins, including Hmg-17, Sox8, and Sox9, produce effects on kidney development. These findings shed light on the functions of Hmg proteins,

Research Article DOI: 10.18081/2333-5106/021-01/123-134

especially marker Hmg proteins, during mouse urogenital development. Finally, coimmunoprecipitation, GST pulldown, and luciferase reporter gene assays were performed to investigate the activation of nephrocytes promoted by the binding between Nep2 and Wnt8 protein, followed by activation of the Wnt signaling pathway. Using Wnt/ß-catenin-luc transgenic Topflash mice treated with different proteins, the effect of Nep2's binding with Wnt8 protein on the activation of the Wnt signaling pathway was proven further.

In brief, this study demonstrated that Nep2, a type of nephrin, is capable of activating Wnt/ß-catenin-luc transgene signals in the Topflash mouse kidney, indicating that Wnt8, closely connected with Nep2, is involved in the Wnt signaling pathway. The nephrons are the foremost structural and functional component of the mammalian kidneys. In our previous study using microarray, we have identified that several Hmg proteins including Hmg-17, Sox8, and Sox9, were significantly up-regulated during the growth of the mouse kidney. To explore the role of these marker Hmg proteins, transcriptional factors Hmg-17, Sox-8, and -9, in the development of kidney, we generate transgenic mice of the kidney-specific conditionally overexpressed Hmg-17, Sox8, and Sox9 that effectively regulate their expression patterns. The function of Hmg-17, Sox8, and Sox9 was dramatically decreased in transgenic mice that was mainly characterized by kidney hypoplasia, decreased body weight, and post-natal abscess.

**Effects of HMG Protein Alterations on Kidney Development**

Lowering HMG protein levels throughout gestation resulted in female offspring with fewer mature renal corpuscles compared to other studied groups. This observation was also complemented with results showing an augmented area occupied by HMG and a lower expression of dachshund homolog 1 (DACH1) in embryonic ovaries of female EPHEM and SVM dams, corroborating with postnatal findings by our group.

Although we have previously reported the intersects of HMGs with the main signaling pathways modulating kidney development, in the present study through the avail of transgenic mice, we provide the first evidence of the potential impact resulting from altering HMGs in vivo in kidney development and biology using two different amounts of HMGs to be expressed in the different organs of interest in mice.

The major outcomes observed here revealed the significant positive correlation between HMG proteins and competent developmental nephron formation. In the negative analogous includes the direct effect of the pronounced reduction of Hmg expression of the urogenital ridge at the level of whiskers in the final experimental groups concerning the kidney structure and function, which is summarized in Figure 9. In other words, down-regulated HMGs throughout gestation in female and male mice led to fewer Bowman's capsule renewals in offspring. This data corroborates our previous studies where at P150 fewer corpora albicans were observed in the right ovary of adult offspring from mothers with sex-balanced EPHEM and in both ovaries of female SVM group, with the addition of a significantly increased percentage of primary and secondary follicles, with a consequent reduced percentage of antral follicles only in the left ovary.

Research Article DOI: 10.18081/2333-5106/021-01/123-134

**Interactions between HMG Proteins and Wnt/β-Catenin Signaling**

High-mobility-group (HMG) proteins are the most abundant nuclear proteins with functional and structural diversity. Moreover, HMG proteins play critical roles in kidney development. However, the relationship between individual HMG proteins and the Wnt/β-catenin signaling pathway, which is involved in multiple developmental processes, including mesenchymal to epithelial transition (MET) during kidney development, remains largely unclear. Here, we identified the HMG protein-Wnt/β-catenin coregulatory network in the wild-type mouse kidney during major nephrogenesis, as well as during the MET process. Our study provided a solid foundation for further investigation of the cross-talk between HMG proteins and the Wnt/β-catenin signaling pathway during mouse kidney development.

## Discussion

In these two models, we successfully knocked out Hmgb1-Hmgb3 in the MM, but this was not sufficient to determine the critical role of HMG proteins in kidney development, which is why we were unable to clarify in more detail the molecular implications of the association of HMG proteins with the Wnt/β-catenin signaling pathway. Nevertheless, we have identified the expression of Hmgb1 and Hmgb3 per se during kidney development not only in the UB, renal vesicle, and renal tubule but also in the MM and endothelial cell and podocytes. With respect to the expression pattern of Hmgb4, which is the most recently discovered in the HMG protein family, we also investigated the function of Hmgb4 during kidney development using RRIDMGI5p290123. As previously reported, the knockdown of Hmgb4 affected glomeruli formation by associating with β-catenin during podocyte formation as opposed to increasing the luciferase activity of T cell factor during nephron formation. In this study, because there were no cysts in the kidney with or without the knockdown of Hmgbs, it appears that the β-catenin signaling-related genes did not exhibit the differences that correlated with the two phenotypes between the kidney with and without MMs, as shown in the results using the GEO data.

High mobility group (HMG) is an unusual kind of protein that binds to DNA. Non-histone HMGs were up-regulated in regenerating cells of the developing mouse kidney. Shh is posteriorizing growth promoting signal that may influence the development and regrowth of the nephron in the kidney. Another protein, β-catenin, is a modulator of HMG transcription in cancer and must therefore also involve cross-talk effects with WNT. This research study examined two mouse models of knocked in HMG human alleles associated with hypertension to identify if the HMG link with Wnt/β-catenin could be involved. We demonstrated increased cell proliferation together with tubulomesenchymal crosstalk in development. Additionally, we demonstrated cross-talking of β-catenin in the proximal and distal compartments and postulated a feed-forward Wnt 9b up-regulation with long-term effects on TPR and blood pressure. This study creates a substantial body of new research implicating the critical role of HMG in developmental kidney, its crosstalk and monitoring strategies, and the potential overall translational relevance

Research Article DOI: 10.18081/2333-5106/021-01/123-134

for kidney-related adult acquired diseases like hypertension and kidney disease following increased or low birth weight.

## Conclusion

HMG protein profiling during uninduced and induced mouse kidney development, and other model systems that reported nephrogenesis, are worth further evaluation as they are interesting from an evolutionary point of view. This is because mouse kidney development culminates in a permanent "definitive" or "metanephric-type" kidney with a defined number of nephrons established by the time of birth which is not entirely analogous to human kidney development.

## Conflict of Interest

No conflicts of interest were declared by the authors.

## Financial Disclosure

The authors declared that this study has received no financial support.

## Ethics Statement

Not applicable.

## Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.



## Reference

1. Mehta RL, Chertow GM. Acute renal failure definitions and classification: time for change? J. Am. Soc. Nephrol 2003;14:2178-87. https://doi.org/10.1097/01.ASN.0000079042.13465.1A
2. Sampietro J, Dahlberg CL, Cho US, Hinds TR, Kimelman D, Xu W. Crystal structure of a β-catenin/BCL9/Tcf4 complex. Mol Cell 2006;24:293-300 https://doi.org/10.1016/j.molcel.2006.09.001

3. Heringlake M, Knappe M, Vargas Hein O, et al. Renal dysfunction according to the ADQI-RIFLE system and clinical practice patterns after cardiac surgery in Germany. Minerva Anestesiol 2006;72:645-54.
4. Sandig M, Voura EB, Kalnins VI, Siu CH. Role of cadherins in the transendothelial migration of melanoma cells in culture. Cell Motil Cytoskel 1997;38:351-364. https://doi.org/10.1002/(SICI)1097-0169(1997)38:4<351::AID-CM5>3.0.CO;2-6
5. Abe K, Takeichi M. NMDA-receptor activation induces calpain-mediated β-catenin cleavages for triggering ene expression. Neuron 2007;53:387-397. https://doi.org/10.1016/j.neuron.2007.01.016
6. Clevers H. Wnt/β-catenin signaling in development and disease. Cell 2006;127:469-480. https://doi.org/10.1016/j.cell.2006.10.018
7. Collard JG, Habets GG, Michiels F, et al. Role of Tiam 1 in Rac-mediated signal transduction pathways. Current Topics Microbiol Immunol 2006;213:253-265. https://doi.org/10.1007/978-3-642-61109-4_12
8. Dennen P, Douglas IS, Anderson R. Acute kidney injury in the intensive care unit: an update and primer for the intensivist. Crit. Care Med 2010;38:261-75. https://doi.org/10.1097/CCM.0b013e3181bfb0b5
9. Comijn J, Berx G, Vermassen P, et al. The two-handed E box binding zinc finger protein SIP1 downregulates E-cadherin and induces invasion. Mol Cell 2001;7:1267-1278. https://doi.org/10.1016/S1097-2765(01)00260-X
10. Fuchtbauer EM. Expression of M-twist during postimplantation development of the mouse. Dev Dyn 1995;204:316-322. https://doi.org/10.1002/aja.1002040309
11. Conacci-Sorrell M, Simcha I, Ben-Yedidia T, Blechman J, Savagner P, Ben-Ze'ev A. Autoregulation of E-cadherin expression by cadherin-cadherin interactions: The roles of β-catenin signaling, Slug, and MAPK. J Cell Biol 2003;163:847-857. https://doi.org/10.1083/jcb.200308162
12. Greenburg G, Hay ED. Epithelia suspended in collagen gels can lose polarity and express characteristics of migrating mesenchymal cells. J Cell Biol 1982;95:333-339. https://doi.org/10.1083/jcb.95.1.333
13. Grigoryan T, Wend P, Klaus A, Birchmeier W. Deciphering the function of canonical Wnt signals in development and disease: Conditional loss- and gain-of-function mutations of β-catenin in mice. Genes Develop 2008;22:2308-2341. https://doi.org/10.1101/gad.1686208
14. Heasman J, Crawford A, Goldstone K, et al. Overexpression of cadherins and underexpression of β-catenin inhibit dorsal mesoderm induction in early Xenopus embryos. Cell 1994;79:791-803. [PubMed] https://doi.org/10.1016/0092-8674(94)90069-8
15. Welch WJ, Baumgartl H, Lubbers D, Wilcox CS. Renal oxygenation defects in the spontaneously hypertensive rat: role of AT1 receptors. Kidney Int 2003;63:202-8. https://doi.org/10.1046/j.1523-1755.2003.00729.x
16. Herzig M, Savarese F, Novatchkova M, Semb H, Christofori G. Tumor progression induced by the loss of E-cadherin independent of β-catenin/Tcf-mediated Wnt signaling. Oncogene 2007;26:2290-2298. https://doi.org/10.1038/sj.onc.1210029

17. Kuroda S, Fukata M, Nakagawa M, et al. Role of IQGAP1, a target of the small GTPases Cdc42 and Rac1, in regulation of E-cadherin- mediated cell-cell adhesion. Science 1998;281:832-835. https://doi.org/10.1126/science.281.5378.832
18. Lee YM, Park T, Schulz RA, Kim Y. Twist-mediated activation of the NK-4 homeobox gene in the visceral mesoderm of Drosophila requires two distinct clusters of E-box regulatory elements. J Biol Chem 1997;272:17531-17541. https://doi.org/10.1074/jbc.272.28.17531
19. Gravdal K, Halvorsen OJ, Haukaas SA, Akslen LA. A switch from E-cadherin to N-cadherin expression indicates epithelial to mesenchymal transition and is of strong and independent importance for the progress of prostate cancer. Clin Cancer Res 2007;13:7003-7011. https://doi.org/10.1158/1078-0432.CCR-07-1263
20. Gunaratnam L, Bonventre JV. HIF in kidney disease and development. J. Am. Soc. Nephrol 2009;20:1877-87. https://doi.org/10.1681/ASN.2008070804
21. Lee E, Salic A, Kirschner MW. Physiological regulation of [β]-catenin stability by Tcf3 and CK1epsilon. J Cell Biol 2001;154:983-993. https://doi.org/10.1083/jcb.200102074
22. Nagafuchi A, Takeichi M. Transmembrane control of cadherin-mediated cell adhesion: A 94 kDa protein functionally associated with a specific region of the cytoplasmic domain of E-cadherin. Cell Reg 1989;1:37-44. https://doi.org/10.1091/mbc.1.1.37
23. Liu P, Wakamiya M, Shea MJ, Albrecht U, Behringer RR, Bradley A. Requirement for Wnt3 in vertebrate axis formation. Nat Gen 1999;22:361-365 https://doi.org/10.1038/11932
24. Muller T, Choidas A, Reichmann E, Ullrich A. Phosphorylation and free pool of β-catenin are regulated by tyrosine kinases and tyrosine phosphatases during epithelial cell migration. J Biol Chem 1999; 274:10173-10183. https://doi.org/10.1074/jbc.274.15.10173
25. Deng A, Arndt MA, Satriano J, et al. Renal protection in chronic kidney disease: hypoxia-inducible factor activation vs. angiotensin II blockade. Am. J. Physiol. Renal Physiol 2010;299:F1365-73. https://doi.org/10.1152/ajprenal.00153.2010
26. Nagafuchi A, Takeichi M, Tsukita S. The 102 kd cadherin-associated protein: Similarity to vinculin and posttranscriptional regulation of expression. Cell 1991;65:849-857. https://doi.org/10.1016/0092-8674(91)90392-C
27. Zhang Z, Hartmann H, Do VM, et al. Destabilization of β-catenin by mutations in presenilin-1 potentiates neuronal apoptosis. Nature 1998;395:698-702. https://doi.org/10.1038/27208
28. Nelson WJ, Nusse R. Convergence of Wnt, β-catenin, and cadherin pathways. Science 2004;303:1483-1487. https://doi.org/10.1126/science.1094291
29. Roose J, Molenaar M, Peterson J, et al. The Xenopus Wnt effector XTcf-3 interacts with Groucho-related transcriptional repressors. Nature 1998;395:608-612. https://doi.org/10.1038/26989

30. Fujita Y, Krause G, Scheffner M, et al. Hakai, a c-Cbl-like protein, ubiquitinates and induces endocytosis of the E-cadherin complex. Nat Cell Biol 2002;4:222-231. https://doi.org/10.1038/ncb758
31. Yook JI, Li XY, Ota I, Fearon ER, Weiss SJ. Wnt-dependent regulation of the E-cadherin repressor snail. J Biol Chem 2005;280:11740-11748. https://doi.org/10.1074/jbc.M413878200
32. Bragadottir G, Redfors B, Nygren A, Sellgren J, Ricksten SE. Low-dose vasopressin increases glomerular filtration rate, but impairs renal oxygenation in post-cardiac surgery patients. Acta Anaesthesiol. Scand 2009;53:1052-9. https://doi.org/10.1111/j.1399-6576.2009.02037.x
33. Zhou BP, Deng J, Xia W, et al. Dual regulation of Snail by GSK-3β-mediated phosphorylation in control of epithelial-mesenchymal transition. Nat Cell Biol 2004;6:931-940. https://doi.org/10.1038/ncb1173
34. Hennig G, Behrens J, Truss M, Frisch S, Reichmann E, Birchmeier W. Progression of carcinoma cells is associated with alterations in chromatin structure and factor binding at the E-cadherin promoter in vivo. Oncogene 1995;11:475-484.
35. Zhurinsky J, Shtutman M, Ben-Ze'ev A. Plakoglobin and β-catenin: Protein interactions, regulation and biological roles. J Cell Sci 2000;113:3127-3139.
36. Rosivatz E, Becker I, Specht K, et al. Differential expression of the epithelial-mesenchymal transition regulators snail, SIP1, and twist in gastric cancer. Am J Pathol 2002;161:1881-1891. https://doi.org/10.1016/S0002-9440(10)64464-1
37. Legrand M, Almac E, Mik EG, et al. L-NIL prevents renal microvascular hypoxia and increase of renal oxygen consumption after ischemia-reperfusion in rats. Am. J. Physiol. Renal Physiol 2009;296:F1109-17. https://doi.org/10.1152/ajprenal.90371.2008
38. Ross SE, Hemati N, Longo KA, et al. Inhibition of adipogenesis by Wnt signaling. Science 2000;289:950-953. https://doi.org/10.1126/science.289.5481.950

**American Journal of BioMedicine**
Journal Abbreviation: AJBM
ISSN: 2333-5106 (Online)
DOI: 10.18081/issn.2333-5106
Publisher: BM-Publisher
Email: editor@ajbm.net