Review Form 1.7

Journal Name:	**International Research Journal of Oncology**
Manuscript Number:	**Ms_IRJO_109384**
Title of the Manuscript:	**Human Homeobox Genes in Development and Cancer**
Type of the Article	**Review Article**

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PART 1: Review Comments

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Compulsory REVISION comments 1. **Is the manuscript important for scientific community?** (Please write few sentences on this manuscript) 2. **Is the title of the article suitable?** (If not please suggest an alternative title) 3. **Is the abstract of the article comprehensive?** 4. **Are subsections and structure of the manuscript appropriate?** 5. **Do you think the manuscript is scientifically correct?** 6. **Are the references sufficient and recent? If you have suggestion of additional references, please mention in the review form.** **(Apart from above mentioned 6 points, reviewers are free to provide additional suggestions/comments)**	**yes** **Yes** **yes** **Yes** **Yes** **Add 5 modern references at last 5 years** **1- Discuss the statement "The Homeobox (HOX) gene family encodes highly conserved homeodomain-containing transcription factors that play a central role in embryonic development and the maintenance of cellular identity critical for adult stem cell differentiation."** **2- This review takes into account the normal pattern of HOX gene expression and the signaling pathways involved in its regulation. How?** **3- What is the benefit of discussing the consequences of dysregulation of the HOX gene in developmental anomalies and carcinogenesis, and the plausibility of the existence of a common mechanism underlying both processes?** **4- Developing a multicellular organism from a single cell is a carefully programmed and controlled process. This is embodied in the embryonic developmental journey from the single-celled zygote (totipotent cell) through a complex process of morphogenesis to reach a fully developed multicellular organism. How?** **5- Countless genes, transcription factors and signaling molecules are used at the right time**	

	for this process to achieve the expected result. Why? 6- Explain why one group of transcription factor-coding genes, the HOX genes, has captured the attention of so many researchers in biomedical disciplines over the years? 7- All Homeobox genes contain a distinct, well-conserved DNA sequence about 180 base pairs long. Explain why? 8- Discuss the following statement "The topographical identity required by their expression patterns is maintained during development in many adult tissues, particularly in ESC-derived adult stem cells, including hematopoietic stem cells (HSCs), mesenchymal stem cells (MSCs), Epithelial stem cells (EpSCs), and neural stem cells. 9- This intrinsic positional specificity is maintained during cell differentiation and provides a mechanism for permanent cell identity and fate restriction in distinct cell types such that the consequences of aberrations in HOX gene expression are lifelong. Why? 10- HOX genes in many animal species are organized as clusters, each containing many genes. This pattern is mirrored in humans, where the 39 HOX genes are organized into four clusters (A, B, C, and D). Why? 11- Discuss the following statement "Many developmental processes are involved in normal human development, including (1) the migration of cells from primitive sites to where they will eventually function, (2) the eventual differentiation of precursor cells into specialized cells, (3) the attachment of groups of cells with similar fates, and (4) sculpting segmental structures and boundaries." 12. Explain the critical role of HOX genes in human development requires tight control of both the timing and pattern of their expression. This occurs mainly at the transcriptional level, but some regulation at the ?level has been documented. 13 These highly coordinated expression patterns of HOX genes indicate a degree of global transcriptional regulation of these gene clusters. However, it has been observed that single	

	HOX genes often retain an anterior-posterior expression profile when randomly combined as transgenes. Why? **14- Transient regulators form gene products, usually proteins, but also miRNAs that bind cis-acting elements to influence the transcription of HOX genes or bind to mRNA to prevent translation of transcription factors. Explain how?** **15- Evidence suggests that the Cdx gene family mediates these signaling pathways, making them direct regulators of gene expression. Explain how?** **16- Discuss the following statement "Retinoic acid signaling involves cell communication through the vitamin A derivative, retinoic acid. This signaling is mediated by a family of nuclear receptors, namely retinoic acid receptors (RARs) and retinoid Retinoic acid, and forms heterodimers called retinoic acid response elements.** **17- RARE regulates the expression of target genes and is found in the regulatory regions of many HOX genes. It is well documented that hypervitaminosis A causes a range of congenital malformations, including anomalies such as situs inversus, faulty hind limbs, spinous bifida, and hypophysis. Thyroid defects in mammals exposed to abnormally high levels of vitamin A during pregnancy Why? Explain this?** **18- Fibroblast growth factors, initially identified as proteins capable of promoting fibroblast proliferation, consist of 22 cell signaling proteins produced by macrophages. These exert multiple functions by binding to and activating fibroblast growth factor receptors Discuss it?** **19- Although most studies indicate that HOX gene regulation occurs primarily through the canonical Wnt signaling pathway, it has been shown that non-canonical Wnt signaling also affects HOX regulation through crosstalk with the canonical Wnt signaling pathway. Explain this?** **19- Although most studies indicate that HOX gene regulation occurs primarily through the canonical Wnt signaling pathway, it has been shown that non-canonical Wnt signaling also**	

	affects HOX regulation through crosstalk with the canonical Wnt signaling pathway. Explain this? **20- Discuss the following statement “The period of expression of HOX genes begins from early life, when they direct ESC differentiation during embryonic development, to later life when they maintain cell identity through ASC-based HOX gene expression. Accordingly, the consequences of HOX gene dysregulation persist.” forever".** **21- Mutations in these genes affect the differentiation of different classes of stem cells (ESC, ASC, and even induced pluripotent stem cells. How is this done?** **22- Discuss the following statement, “Developmental disorders associated with HOX genes arise from germ-line mutations in the affected genes and are heritable. Reflecting the highly conserved nature of HOX genes, human phenotypes tend to resemble homozygous mouse mutations.”**	

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Minor REVISION comments **1. Is language/English quality of the article suitable for scholarly communications?**	Yes	
Optional/General comments	**23- The duplication and divergence of ancestral HOX genes in vertebrates has allowed functional redundancy such that each similar group, consisting of 2 to 4 genes, shares the ability to influence the final phenotype of the embryo. Explain this? how?** **24- In humans, the wing-associated integration site (WNT) signaling pathways comprise a family of nineteen proteins whose signal transduction regulates a variety of cellular processes, including fate determination, cell migration, cell polarity, neuronal patterning, and organogenesis during embryonic development. Explain how the mechanism works?** **25- Accordingly, the vast repertoire of stem cells and their descendants creates endless oncogenic potential in the context of HOX gene dysregulation. This is particularly important in the regeneration of systems with high turnover such as hematopoietic tissues. How?** **26- Discuss the following statement: "Stem cells are the only ones that persist long enough in tissues to be able to go through the lengthy sequence of successive mutations and selection required for the concept of multistage carcinogenesis."** **27- HSCs are the basis of hematopoiesis, and generate all distinct and functional hematopoietic lineages. Explain this?** **28- Discuss the following statement "Chromosomal translocations that create fusion genes usually underlie the transcriptional disturbance observed in many leukemias. Changes in HOX gene expression associated with chromosomal translocations have been demonstrated in acute myelogenous leukemia (AML).** **29- Although the mechanisms underlying many cancers have not been fully elucidated, some therapeutic options, including gene therapy, small molecule inhibitors or RNA interference (RNAi), and epigenetic modification to modify transcription, are under study**	

	Already RNAi is being evaluated as an inhibitor of HOXB7, a gene silencing mechanism to improve KBF prostate cancer cell growth? **30. The regulated and timely pattern of HOX gene expression that extends from embryonic development to adulthood is a compelling example of the general dynamics of gene expression and reveals the potential consequences of its disruption. In addition, the fact that certain molecular pathways contribute to both normal development and disease suggests that wellness is maintained within a precisely regulated balance. How is this done?** **31- Discuss the following statement, "Epigenetic reprogramming (DNA methylation and histone acetylation) of HOX genes to regulate their expression can also be used in the treatment of cancers in which HOX dysregulation is a driving force."** **32- There is still much that needs to be clarified about the complete profile of HOX gene functions and regulation, which will hopefully open new horizons for more intervention targets, especially in the perpetual battle against cancer. What do you think of this sentence?** **33- Is it possible to add the error percentage and p-value values for the measurements and what are their amounts?**	

PART 2:

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Are there ethical issues in this manuscript?	*(If yes, Kindly please write down the ethical issues here in details)* Not exist	

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