

# Master regulator genes and their impact on major diseases

**Wanwan Cai** <sup>Equal first author, 1</sup>, **Wanbang Zhou** <sup>Equal first author, 2</sup>, **Zhe Han** <sup>3</sup>, **Junrong Lei** <sup>2</sup>, **Jian Zhuang** <sup>4</sup>, **Ping Zhu** <sup>4</sup>, **Xiushan Wu** <sup>1</sup>, **Wuzhou Yuan** <sup>Corresp. 1</sup>

<sup>1</sup> The Center for Heart Development, State Key Laboratory of Development Biology of Freshwater Fish, Key Laboratory of MOE for Development Biology and Protein Chemistry, College of Life Sciences, Hunan Normal University, Changsha, Hunan, China

<sup>2</sup> College of physical education, Hunan Normal University, Changsha, Hunan, China

<sup>3</sup> Children's National Medical Center, 111 Michigan Ave, Princess Margaret Cancer Centre, Michigan, Washington, USA

<sup>4</sup> Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Department of Cardiac Surgery, Guangzhou, Guangdong, China

Corresponding Author: Wuzhou Yuan  
Email address: yuanwuzhou@aliyun.com

Master regulator genes (MRGs) have become a hot topic in recent decades. They not only affect the development of tissue and organ systems but also play a role in other signal pathways by regulating additional MRGs. Because a MRG can regulate the concurrent expression of several genes, its mutation often leads to major diseases. Moreover, the occurrence of many tumors and cardiovascular diseases are closely related to MRG changes. With the advancements in omics research, an increasing amount of investigations will be directed toward MRGs because their regulation involves all aspects of an individual's development. This review focuses on the definition and classification of MRGs as well as their influence on disease regulation.

# Master regulator genes and their impact on major diseases

Wanwan Cai<sup>1#</sup>, Wanbang Zhou<sup>2#</sup>, Zhe Han<sup>3</sup>, Junrong Lei<sup>2</sup>, Jian Zhuang<sup>4</sup>, Ping Zhu<sup>4</sup>, Xiushan Wu<sup>1\*</sup>, Wuzhou Yuan<sup>1\*</sup>

1 The Center for Heart Development, State Key Laboratory of Development Biology of Freshwater Fish, Key Laboratory of MOE for Development Biology and Protein Chemistry, College of Life Sciences, Hunan Normal University, Changsha, Hunan 410081, China;

2 College of physical education, Hunan Normal University, Changsha, Hunan 410081, China;

3 Center for Cancer and Immunology Research, Children's National Medical Center, 111 Michigan Ave. NW, Washington, DC, 20010, USA.

4 Department of Cardiac Surgery, Guangdong Cardiovascular Institute, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong 510100, China

<sup>#</sup> These authors contributed equally to this work.

<sup>\*</sup> Corresponding authors

Wuzhou Yuan: [yuanwuzhou@aliyun.com](mailto:yuanwuzhou@aliyun.com)

Xiushan Wu: [xiushanwu@yahoo.com](mailto:xiushanwu@yahoo.com)

# ABSTRACT

Master regulator genes (MRGs) have become a hot topic in recent years. They not only affect the development of tissue and organ systems but also play a role in other signal pathways by regulating additional MRGs. Because a MRG can regulate the concurrent expression of several genes, its mutation often leads to major diseases. Moreover, the occurrence of many tumors and cardiovascular diseases are closely related to MRG changes. With the advancements in omics research, an increasing amount of investigations will be directed toward MRGs because their regulation involves all aspects of an individual's development. This review focuses on the definition and classification of MRGs as well as their influence on disease regulation.

**Keywords:** master regulator genes; signal pathway; tumor diseases; cardiovascular disease

# 1. INTRODUCTION

Since the discovery of the master regulator genes (MRGs) and the powerful functions of these genes involving in all aspects of tissue and organ development, the study of MRGs has been more and more extensive, and an increasing number of new MRGs has been reported to play key roles in major clinical diseases.. However, the definition of the MRG is still indistinct and ambiguous, and a systematic and comprehensive review about MRGs is lacking. In this review, we proposed a novel definition and systematic classification of MRGs, and summarized the role of MRGs in major clinical diseases. The subject presented in this article is written in a descriptive manner instead of a systematic review so that clinicians outside our professional field can understand the basic characteristics of MRGs and their significant effects on clinical diseases.

# 2. WHAT IS THE MASTER REGULATOR GENE ?

The term “master regulator gene” introduced by Susumu Ohno in 1979, refers to “the gene at the top of the regulatory hierarchy, which should not be affected by the regulation of any other genes” (S, 1978). However, with the increasingly extensive and in-depth study of master regulator genes

(MRGs) in recent decades, this definition is no longer an absolute. Many studies have shown that some MRGs can regulate others. For example, *mdm2* is the master regulator of tumor suppressor protein p53 (Momand et al., 2000), while the *p53* gene is a master regulator of diverse cellular processes and a potential therapeutic target for cancer (Farnebo et al., 2010); and *snail* is the master regulator of epithelial-mesenchymal transition, but it is regulated by *Pak1* through phosphorylation (Takahashi et al., 2013), which implicates *Pak1* as a master regulator of epithelial-mesenchymal transition (Yang et al., 2005).

It has been reported that MRGs could play a key role via multiple signal pathways. For example, adenosine monophosphate-activated protein kinase (AMPK) regulates the energy balance inside cells by inhibiting adenosine triphosphate (ATP) consumption in the anabolic pathway and enhancing ATP synthesis in the catabolic pathway. When activated by external metabolic pressure, AMPK regulates a complex downstream signal cascade, promoting efficient energy production within the cells (Witczak et al., 2008). Another example is the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) signaling pathway. Although this pathway can be considered as a master regulator for cancer (Xia and Xu, 2015), mTOR is also considered a MRG of metabolism (Kim and Guan, 2015; Zeng, 2017). Furthermore, it has been reported that the genes for the three transcription factors Sox2, Oct3/4, and Nanog have been identified as the MRGs that regulate mammalian embryogenesis, embryonic stem cell self-renewal, and pluripotency. These MRGs can bind to enhancer elements in pluripotent embryonic stem cells (ESCs) and recruit mediators to form unusual enhancer domains, which are called super-enhancers. When the MRGs and mediators are simultaneously occupied, the expression programs for most genes in ESCs become co-activated (Rizzino, 2008; Whyte et al., 2013). To summarize, MRGs can be redefined as genes that are expressed at the beginning of a developmental lineage or in specific cell types that control multiple downstream genes by directly regulating the expression of a series of genes or interacting with other master genes and signaling pathways to form super-enhancers that participate in the specification of the development process of one or more tissues, organs, or cell

lineages. If a MRG is misexpressed, this could profoundly impact the fate of cells that regulate the formation of other lineages (Chan and Kyba, 2013).

### 3. OVERVIEW OF MRGs

A survey of >2,000 articles was carried out using the National Center for Biotechnology Information PubMed database (<https://www.ncbi.nlm.nih.gov/pubmed/>) by searching the keyword “master regulator gene”. After screening the contents of the abstracts of these literatures, we found that 889 articles quoting MRGs covered most species. Key words were extracted and recorded during the abstract reading, including the properties of the MRGs, the signaling pathways involved, the tissues or organs involved, and the diseases caused, etc. All the data was collated and considered effective. If multiple references mentioned a same MRG, we selected recently published papers or well-known journals for reference. These MRGs were systematically classified as either (1) whole-family MRGs, (2) signal pathway MRGs, or (3) tissue- or organ-specific MRGs.

Family MRGs refer to a gene family where all members are MRGs. There are two types: either all members have the same function, such as the HOX, MTA, and SREBP families; or different members in the same family may possess different functions, such as the GATA gene family. The HOX family MRGs are all involved in developmental processes, such as embryogenesis and hematopoiesis (Candini et al., 2015; Grier et al., 2005; Magnusson et al., 2007; McGonigle et al., 2008; Rice and Licht, 2007; Vogel et al., 2016; Zhang et al., 2015). In mammals, the HOX network consists of 39 genes that exhibit a high degree of sequence similarity, particularly in the homeobox domain. Many of the chromosomal translocations associated with acute leukemias involve HOX genes, such as mixed lineage leukemia, which leads to the inappropriate expression of specific HOX gene subsets (Dickson et al., 2009). In the GATA family, where each member has a different function, GATA1 and GATA2 regulate erythropoiesis and hematopoiesis as MRGs (Kang et al., 2012; Katsumura et al., 2014; Philipsen, 2013), GATA3 is an immune response MRG (Li et al., 2015; Nicol et al., 2016), and GATA4 regulates embryonic pancreas development (Kondratyeva et al., 2017). Table 1 lists 18 major

family MRGs. Among them, the CDX, CDK, HSF, MTA, SREBP, Rho, HNF, IL families and the Rab GTPase superfamily contain genes with the same functions. In the PLK, PAX, TBX, SOX, RUNX, IRF, Bcl, and C/EBP families, each family member shares similar functions but also performs their own distinct role.

The second type of MRGs involve signaling pathways. In this type, one of the members in the signal pathway is the MRG, such as AMPK from the AMPK signal pathway, which is known as a master regulator of cellular energy metabolism due to its role in regulating glucose, lipid, and protein metabolism. AMPK is an evolutionarily conserved master regulator of metabolism and a therapeutic target in type 2 diabetes. As an energy sensor, AMPK activity is responsive to both metabolic inputs, i.e., the ratio of AMP to ATP and numerous hormonal cues (Cunningham et al., 2014; Witczak et al., 2008). More often, the entire signaling pathway acts as the MRG to regulate the development of a series of tissues and organs. For example, the mTOR signaling pathway is a master regulator of cell growth, proliferation and survival, metabolism, and skeletal muscle production in eukaryotes (Donnelly et al., 2017; Zeng, 2017). mTOR belongs to the PI3K-related protein kinase family. The mTOR signaling pathway plays a crucial role in the functional recovery of central nervous system trauma, especially for axon regeneration and autophagy, which has an extensive association with apoptosis. Significantly, this pathway is receiving novel concern for its role in the repair and regeneration of traumatic central nervous system injuries, such as traumatic brain injury and spinal cord injury (Lin et al., 2017). The major signaling pathways involved MRGs are presented in Table 2. For example, the transforming growth factor (TGF)  $\beta$  signaling pathway is the master regulator of the respiratory system, epithelial-mesenchymal transition and metastasis, and cancer development; the PI3K-AKT-mTOR signaling pathway is the master regulator of cancer; Hedgehog signaling is the master regulator of cell differentiation; and the NF- $\kappa$ B signaling pathway is the master regulator of innate immune and inflammatory signals. It is noteworthy that the Wnt signaling pathway is not only the master regulator of cell development, cell polarization, and brain invasion but also the master regulator of liver-region and multiple renin-angiotensin system genes.

The third type of MRGs are tissue- or organ-specific MRGs that regulate the development of different tissue and organ systems. Among them, SCL/TAL1 (Courtial et al., 2011; Wehrspaun et al., 2015), VEGF (Danese, 2008), and PU.1 (Yang et al., 2012) are the MRGs of hematopoiesis; Sim1 (Eaton and Glasgow, 2006) and Gcm (Cattenoz and Giangrande, 2016) are the MRGs of *Drosophila* neurodevelopment; FOXM1, Blimp1, Oct4, and Myc are the MRGs that regulate the cell cycle (Jeffery et al., 2017; Zona et al., 2014), B-cell differentiation to plasma cells (John and Garrett-Sinha, 2009; Vrzalikova et al., 2012; Yang et al., 2012), embryonic stem cells (Samardzija et al., 2017; Weeks KL1, 2012 ), and cell performance (Grifoni and Bellosta, 2015; Holmberg Olausson et al., 2012; Kazan and Manners, 2013), respectively; CTCF is the MRG of human epigenetic and genomic spatial tissue (Golan-Mashiach et al., 2012); and FOXj1 is the MRG of the ciliary formation program (Yu et al., 2008). In bacteria, the MRGs include SinR (Chu et al., 2006; Stowe et al., 2014), CtrA (Gora et al., 2010; Laub et al., 2002; Pini et al., 2015), FlhDC (Chatterjee et al., 2015; Cui et al., 2008; Stafford et al., 2005), Fur (González et al., 2012; Huja et al., 2014), CsgD (Ogasawara et al., 2010; Wen et al., 2017), Spo0A (Fujita and Losick, 2005; Wolański et al., 2014), CcpA (Muscariello et al., 2013; Weeks KL1, 2012 ), LuxR (Ball et al., 2017; Pompeani et al., 2008), and WOR1 (Zhang et al., 2014). Other tissue- and organ-specific MRGs are listed in Supplementary Table 1.

#### 4. REGULATION OF MAJOR DISEASES BY THE MRGs

Since MRGs can concurrently regulate the expression of hundreds of genes, their expression levels are tightly controlled because misexpression or overexpression will exert a considerable impact on the development of affected organisms, resulting in runaway or uncontrolled metabolism and abnormal development in humans.

##### *MRGs regulation of tumors*

MRGs have been implicated in the occurrence of different tumors, including germ cell tumors, ovarian cancer, colon cancer, rectal cancer, and lung cancer. For example, SOX9, GATA4, PDX1, PTF1a, HNF1b, and GRP78 are master regulators of pancreatic cancer

(Kondratyeva et al., 2017); while Srebp2 (Krycer et al., 2010) and E2F8 (Rohde et al., 1996) are MRGs of prostate cancer; and CDX2 is the master regulator of gastric cancer (Shiotani et al., 2008). Nuclear receptors are liver cancer-related (Jakobsson et al., 2012); PD-L1, TGF- $\beta$ 1, and IL-10 are the master regulators of cervical cancer (Qin et al., 2017); and Oct4A is the master regulator of ovarian cancer (Samardzija et al., 2017).

The most extensively studied MRGs are associated with breast cancer and leukemia. Breast cancer is the most common malignant tumor in women. It has been reported that RUNX1 encodes the transcription factor of the RUNX family, which was recently discovered to be a new mutant gene in human breast cancer. It was reported that Runx1 was expressed in all subpopulations of mouse mammary epithelial cells (MECs) except for secretory alveolar cells. The conditional knockout of Runx1 in the MECs resulted in the reduction of luminal MECs. Mainly due to a significant reduction in estrogen receptors (ERs), this phenotype could be rescued by the absence of Trp53 or Rb1. The underlying molecular mechanism was explained by RUNX1 inhibiting the expression of *Elf5* (the dominant gene in alveolar cells) and regulating the involvement of mature transcription factor or cofactor genes (such as *Foxa1* and *Cited1*) in the processes of ER synthesis (van Bragt et al., 2014). Many other MRGs have been reported as associated with the development of breast cancer, including the HOX gene family, sox4, Runx2, AMPK, p53, TGF- $\beta$ , microRNA, KDM4B, p16INK4A, BACH1, Snai1, HMGA1, SATB1, HSP90, TRB3, Ddx5 and Ddx17, FGFR2, and AGTR2 (Supplementary Table 2).

Another type of widely studied cancer is leukemia, a malignant clonal disease of hematopoietic stem cells. Due to uncontrolled proliferation, differentiation disorder, and blocked apoptosis, clonal leukemia cells proliferate and accumulate in the bone marrow and other hematopoietic tissues, infiltrate other non-hematopoietic tissues and organs, and inhibit normal hematopoietic function. Acute lymphoblastic leukemia (ALL) is the most common form of childhood cancer and is characterized by impaired lymphocyte differentiation, resulting in the accumulation of immature progenitor cells in the bone marrow, peripheral blood, and occasionally the central nervous system. Although ALL cure rates are close to 90%, it remains



the leading cause of cancer-related mortality in children and young adults. Another extremely prevalent form of leukemia is B-cell precursor (BCP)-ALL, which represents 85% of cases, while the remaining 15% involve T-cell precursors. It was reported that BCP-ALL might be caused by the synergistic regulation of transcription factors, such as RUNX1, IKZF1, E2A, EBF1, and PAX5 (Tijchon et al., 2012). The other MRGs associated with leukemia include HOX, GATA, CDX, Pax, C/EBP $\beta$  genetic lesions, and key transcriptional targets and pathways (Supplementary Table 2).

### ***Influence of MRGs on cardiovascular diseases***

Because cardiovascular disease is the leading cause of death in humans, elucidation of the associated role of MRGs is of immense clinical and social value for the effective prevention and treatment of cardiovascular diseases. The MRGs related to heart disease (Table 3) include TBX5, NuRD, SREBP, MyoD, Class IB PI3K p110 genetic lesions, PI3K, and PITX2, which mainly regulate congenital heart disease, metabolic heart disease, heart failure, arrhythmia, etc. Vascular-related MRGs, which include PKC $\delta$ , VEGF, SCL/TAL1, PPAR gamma, PGC-1 $\alpha$ , SOX9, myocardin, FLYWCH1, PSORSIC3, G3BP1, and Etv2, mainly regulate thrombosis, anemia, atherosclerosis, vascular calcification, coronary artery disease, chronic vascular disease, etc. Others, like, Klotho, thyroid hormones and thyroid-stimulating hormone, and CST were also reported as master regulators of cardiovascular disease.

There are some reports on the progress of research investigating the influence of MRGs on diseases such as inflammatory bowel disease, cartilage disease, and human diseases related to fibroblasts. Thus, the influence of MRGs in human diseases has permeated every aspect, and MRGs play a vital role in the clinical research and treatment of human diseases. However, how the MRGs can be used more comprehensively to solve the thorny problems in human diseases is an arduous task at present.

## **5. OUTLOOK**

With the expanding research in omics, including fields such as genomics, functional genomics, comparative genomics, structural genomics, transcriptomics, proteomics, and metabolomics,

research pertaining to MRGs will continue advancing because the involvement of master gene regulation in all aspects of individual development is becoming apparent. Here we demonstrated that MRGs fell within three operating motifs: (1) whole-family MRGs, (2) pathway MRGs, and (3) tissue- or organ-specific MRGs. The formidable function of an MRG lies not only in its regulation of the concurrent expression of hundreds of genes but also the diversity of its functions. For the application of MRGs in clinical medical treatment, it is necessary to strengthen the in-depth understanding of disease-related MRGs to develop target-specific and more effective treatment programs.

# **ACKNOWLEDGMENTS**

This study was supported in part by grants from the National Natural Science Foundation of China (Nos.: 81370451, 81470449, 81670290, 81570279), the Cooperative Innovation Center of Engineering and New Products for Developmental Biology of Hunan Province (No. 2013-448-6).

245

# 246 REFERENCES

- 247 Ball, A.S., Chaparian, R.R., and van Kessel, J.C. (2017). Quorum Sensing Gene Regulation by  
248 LuxR/HapR Master Regulators in Vibrios. *Journal of bacteriology* 199, e00105-00117.
- 249 Candini, O., Spano, C., Murgia, A., Grisendi, G., Veronesi, E., Piccinno, M.S., Ferracin, M.,  
250 Negrini, M., Giacobbi, F., Bambi, F., *et al.* (2015). Mesenchymal Progenitors Aging Highlights a  
251 miR-196 Switch Targeting HOXB7 as Master Regulator of Proliferation and Osteogenesis.  
252 *STEM CELLS* 33, 939-950.
- 253 Cattenoz, P.B., and Giangrande, A. (2016). Revisiting the role of the Gcm transcription factor,  
254 from master regulator to Swiss army knife. *Fly (Austin)* 10, 210-218.
- 255 Chan, S.S.-K., and Kyba, M. (2013). What is a Master Regulator? *J Stem Cell Res Ther* 3, 114.
- 256 Chatterjee, A., Cui, Y., and Chatterjee, A.K. (2015). Correction for Chatterjee et al., RsmC of  
257 *Erwinia carotovora* subsp. *carotovora* Negatively Controls Motility, Extracellular Protein  
258 Production, and Virulence by Binding FlhD and Modulating Transcriptional Activity of the  
259 Master Regulator, FlhDC. *Journal of bacteriology* 197, 3848-3848.
- 260 Chu, F., Kearns, D.B., Branda, S.S., Kolter, R., and Losick, R. (2006). Targets of the master  
261 regulator of biofilm formation in *Bacillus subtilis*. *Molecular Microbiology* 59, 1216-1228.
- 262 Courtial, N., Smink, J.J., Kuvardina, O.N., Leutz, A., Göthert, J.R., and Lausen, J. (2011). Tall  
263 regulates osteoclast differentiation through suppression of the master regulator of cell fusion DC-  
264 STAMP. *The FASEB Journal* 26, 523-532.
- 265 Cui, Y., Chatterjee, A., Yang, H., and Chatterjee, A.K. (2008). Regulatory network controlling  
266 extracellular proteins in *Erwinia carotovora* subsp. *carotovora*: FlhDC, the master regulator of  
267 flagellar genes, activates rsmB regulatory RNA production by affecting gacA and hexA (IrhA)  
268 expression. *Journal of bacteriology* 190, 4610-4623.
- 269 Cunningham, K.A., Bouagnon, A.D., Barros, A.G., Lin, L., Malard, L., Romano-Silva, M.A.,  
270 and Ashrafi, K. (2014). Loss of a neural AMP-activated kinase mimics the effects of elevated  
271 serotonin on fat, movement, and hormonal secretions. *PLoS Genet* 10, e1004394-e1004394.
- 272 Danese, S. (2008). VEGF in inflammatory bowel disease: A master regulator of mucosal  
273 immune-driven angiogenesis. *Digestive and Liver Disease* 40, 680-683.
- 274 Dickson, G.J., Lappin, T.R., and Thompson, A. (2009). Complete Array of HOX Gene  
275 Expression by RQ-PCR. In *Leukemia: Methods and Protocols*, C.W. Eric So, ed. (Totowa, NJ:  
276 Humana Press), pp. 369-393.
- 277 Donnelly, S., Huston, W.M., Johnson, M., Tiberti, N., Saunders, B., O'Brien, B., Burke, C.,  
278 Labbate, M., and Combes, V. (2017). Targeting the master regulator mTOR: a new approach to  
279 prevent the neurological of consequences of parasitic infections? *Parasit Vectors* 10, 581-581.
- 280 Eaton, J.L., and Glasgow, E. (2006). The zebrafish bHLH PAS transcriptional regulator, single-  
281 minded 1 (sim1), is required for isotocin cell development. *Developmental Dynamics* 235, 2071-  
282 2082.
- 283 Farnebo, M., Bykov, V.J.N., and Wiman, K.G. (2010). The p53 tumor suppressor: A master  
284 regulator of diverse cellular processes and therapeutic target in cancer. *Biochemical and*

Biophysical Research Communications 396, 85-89.

Fujita, M., and Losick, R. (2005). Evidence that entry into sporulation in *Bacillus subtilis* is governed by a gradual increase in the level and activity of the master regulator Spo0A. *Genes Dev* 19, 2236-2244.

Golan-Mashiach, M., Grunspan, M., Emmanuel, R., Gibbs-Bar, L., Dikstein, R., and Shapiro, E. (2012). Identification of CTCF as a master regulator of the clustered protocadherin genes. *Nucleic Acids Res* 40, 3378-3391.

González, A., Bes, M.T., Valladares, A., Peleato, M.L., and Fillat, M.F. (2012). FurA is the master regulator of iron homeostasis and modulates the expression of tetrapyrrole biosynthesis genes in *Anabaena* sp. PCC 7120. *Environmental Microbiology* 14, 3175-3187.

Gora, K.G., Tsokos, C.G., Chen, Y.E., Srinivasan, B.S., Perchuk, B.S., and Laub, M.T. (2010). A cell-type-specific protein-protein interaction modulates transcriptional activity of a master regulator in *Caulobacter crescentus*. *Mol Cell* 39, 455-467.

Grier, D.G., Thompson, A., Kwasniewska, A., McGonigle, G.J., Halliday, H.L., and Lappin, T.R. (2005). The pathophysiology of HOX genes and their role in cancer. *J Pathol* 205, 154-171.

Grifoni, D., and Bellosta, P. (2015). *Drosophila* Myc: A master regulator of cellular performance. *Biochim Biophys Acta* 1849, 570-581.

Holmberg Olausson, K., Nistér, M., and Lindström, M.S. (2012). p53 -Dependent and -Independent Nucleolar Stress Responses. *Cells* 1, 774-798.

Huja, S., Oren, Y., Biran, D., Meyer, S., Dobrindt, U., Bernhard, J., Becher, D., Hecker, M., Sorek, R., and Ron, E.Z. (2014). Fur is the master regulator of the extraintestinal pathogenic *Escherichia coli* response to serum. *MBio* 5, e01460-01414.

Jakobsson, T., Treuter, E., Gustafsson, J.-Å., and Steffensen, K.R. (2012). Liver X receptor biology and pharmacology: new pathways, challenges and opportunities. *Trends in Pharmacological Sciences* 33, 394-404.

Jeffery, J.M., Kalimutho, M., Johansson, P., Cardenas, D.G., Kumar, R., and Khanna, K.K. (2017). FBXO31 protects against genomic instability by capping FOXM1 levels at the G2/M transition. *Oncogene* 36, 1012-1022.

John, S.A., and Garrett-Sinha, L.A. (2009). Blimp1: A conserved transcriptional repressor critical for differentiation of many tissues. *Experimental Cell Research* 315, 1077-1084.

Kang, Y.-A., Sanalkumar, R., O'Geen, H., Linnemann, A.K., Chang, C.-J., Bouhassira, E.E., Farnham, P.J., Keles, S., and Bresnick, E.H. (2012). Autophagy Driven by a Master Regulator of Hematopoiesis. *Molecular and Cellular Biology* 32, 226-239.

Katsumura, K.R., Yang, C., Boyer, M.E., Li, L., and Bresnick, E.H. (2014). Molecular basis of crosstalk between oncogenic Ras and the master regulator of hematopoiesis GATA-2. *EMBO reports* 15, 938-947.

Kazan, K., and Manners, J.M. (2013). MYC2: The Master in Action. *Molecular Plant* 6, 686-703.

Kim, Y.C., and Guan, K.-L. (2015). mTOR: a pharmacologic target for autophagy regulation. *The Journal of Clinical Investigation* 125, 25-32.

Kondratyeva, L.G., Chernov, I.P., Zinovyeva, M.V., Kopantzev, E.P., and Sverdlov, E.D. (2017). Expression of master regulatory genes of embryonic development in pancreatic tumors. *Doklady*

Biochemistry and Biophysics 475, 250-252.

Krycer, J.R., Sharpe, L.J., Luu, W., and Brown, A.J. (2010). The Akt–SREBP nexus: cell signaling meets lipid metabolism. *Trends in Endocrinology & Metabolism* 21, 268-276.

Laub, M.T., Chen, S.L., Shapiro, L., and McAdams, H.H. (2002). Genes directly controlled by CtrA, a master regulator of the *Caulobacter* cell cycle. *Proc Natl Acad Sci U S A* 99, 4632-4637.

Li, R., Campos, J., and Iida, J. (2015). A Gene Regulatory Program in Human Breast Cancer. *Genetics* 201, 1341-1348.

Lin, J., Huo, X., and Liu, X. (2017). "mTOR Signaling Pathway": A Potential Target of Curcumin in the Treatment of Spinal Cord Injury. *Biomed Res Int* 2017, 1634801-1634801.

Magnusson, M., Brun, A.C.M., Miyake, N., Larsson, J., Ehinger, M., Bjornsson, J.M., Wutz, A., Sigvardsson, M., and Karlsson, S. (2007). HOXA10 is a critical regulator for hematopoietic stem cells and erythroid/megakaryocyte development. *Blood* 109, 3687-3696.

McGonigle, G.J., Lappin, T.R.J., and Thompson, A. (2008). Grappling with the HOX network in hematopoiesis and leukemia. In *Front Biosci*, pp. 4297-4308.

Momand, J., Wu, H.-H., and Dasgupta, G. (2000). MDM2 — master regulator of the p53 tumor suppressor protein. *Gene* 242, 15-29.

Muscariello, L., Marino, C., Capri, U., Vastano, V., Marasco, R., and Sacco, M. (2013). CcpA and three newly identified proteins are involved in biofilm development in *Lactobacillus plantarum*. *Journal of Basic Microbiology* 53, 62-71.

Nicol, L., Wilkie, H., Gossner, A., Watkins, C., Dalziel, R., and Hopkins, J. (2016). Variations in T cell transcription factor gene structure and expression associated with the two disease forms of sheep paratuberculosis. *Veterinary Research* 47, 83.

Ogasawara, H., Yamamoto, K., and Ishihama, A. (2010). Regulatory role of MlrA in transcription activation of *csgD*, the master regulator of biofilm formation in *Escherichia coli*. *FEMS Microbiology Letters* 312, 160-168.

Philipsen, S. (2013). A new twist to the GATA switch. *Blood* 122, 3391-3392.

Pini, F., De Nisco, N.J., Ferri, L., Penterman, J., Fioravanti, A., Brilli, M., Mengoni, A., Bazzicalupo, M., Viollier, P.H., Walker, G.C., *et al.* (2015). Cell Cycle Control by the Master Regulator CtrA in *Sinorhizobium meliloti*. *PLoS Genet* 11, e1005232-e1005232.

Pompeani, A.J., Irgon, J.J., Berger, M.F., Bulyk, M.L., Wingreen, N.S., and Bassler, B.L. (2008). The *Vibrio harveyi* master quorum-sensing regulator, LuxR, a TetR-type protein is both an activator and a repressor: DNA recognition and binding specificity at target promoters. *Molecular microbiology* 70, 76-88.

Qin, Y., Ekmekcioglu, S., Forget, M.-A., Szekvolgyi, L., Hwu, P., Grimm, E.A., Jazaeri, A.A., and Roszik, J. (2017). Cervical Cancer Neoantigen Landscape and Immune Activity is Associated with Human Papillomavirus Master Regulators. *Front Immunol* 8, 689-689.

Rice, K.L., and Licht, J.D. (2007). HOX deregulation in acute myeloid leukemia. *J Clin Invest* 117, 865-868.

Rizzino, A. (2008). Transcription factors that behave as master regulators during mammalian embryogenesis function as molecular rheostats. *Biochemical Journal* 411, e5-e7.

Rohde, M., Warthoe, P., Gjetting, T., Lukas, J., Bartek, J., and Strauss, M. (1996). The

retinoblastoma protein modulates expression of genes coding for diverse classes of proteins including components of the extracellular matrix. *Oncogene* 12, 2393-2401.

S, O. (1978). Major sex-determining genes. *Monogr Endocrinol*, 1-140.

Samardzija, C., Greening, D.W., Escalona, R., Chen, M., Bilandzic, M., Luwor, R., Kannourakis, G., Findlay, J.K., and Ahmed, N. (2017). Knockdown of stem cell regulator Oct4A in ovarian cancer reveals cellular reprogramming associated with key regulators of cytoskeleton-extracellular matrix remodelling. *Sci Rep* 7, 46312-46312.

Shiotani, A., Kamada, T., Yamanaka, Y., Manabe, N., Kusunoki, H., Hata, J., and Haruma, K. (2008). Sonic hedgehog and CDX2 expression in the stomach. *Journal of Gastroenterology and Hepatology* 23, S161-S166.

Stafford, G.P., Ogi, T., and Hughes, C. (2005). Binding and transcriptional activation of non-flagellar genes by the *Escherichia coli* flagellar master regulator FlhD2C2. *Microbiology (Reading, England)* 151, 1779-1788.

Stowe, S.D., Olson, A.L., Losick, R., and Cavanagh, J. (2014). Chemical shift assignments and secondary structure prediction of the master biofilm regulator, SinR, from *Bacillus subtilis*. *Biomol NMR Assign* 8, 155-158.

Takahashi, R.-u., Takeshita, F., Honma, K., Ono, M., Kato, K., and Ochiya, T. (2013). Ribophorin II regulates breast tumor initiation and metastasis through the functional suppression of GSK3 $\beta$ . *Sci Rep* 3, 2474-2474.

Tijchon, E., Havinga, J., van Leeuwen, F.N., and Scheijen, B. (2012). B-lineage transcription factors and cooperating gene lesions required for leukemia development. *Leukemia* 27, 541.

van Bragt, M.P.A., Hu, X., Xie, Y., and Li, Z. (2014). RUNX1, a transcription factor mutated in breast cancer, controls the fate of ER-positive mammary luminal cells. *Elife* 3, e03881-e03881.

Vogel, M., Velleuer, E., Schmidt-Jiménez, L.F., Mayatepek, E., Borkhardt, A., Alawi, M., Kutsche, K., and Kortüm, F. (2016). Homozygous HOXB1 loss-of-function mutation in a large family with hereditary congenital facial paresis. *American Journal of Medical Genetics Part A* 170, 1813-1819.

Vrzalikova, K., Woodman, C.B.J., and Murray, P.G. (2012). BLIMP1 $\alpha$ , the master regulator of plasma cell differentiation is a tumor suppressor gene in B cell lymphomas. *Biomedical papers* 156, 1-6.

Weeks KL1, G.X., Du XJ, Boey EJ, Matsumoto A, Bernardo BC, Kiriazis H, Cemerlang N, Tan JW, Tham YK, Franke TF, Qian H, Bogoyevitch MA, Woodcock EA, Febbraio MA, Gregorevic P, McMullen JR (2012 ). Phosphoinositide 3-kinase p110 $\alpha$  is a master regulator of exercise-induced cardioprotection and PI3K gene therapy rescues cardiac dysfunction. *Circ Heart Fail* 5, 523-534.

Wehrspaun, C.C., Haerty, W., and Ponting, C.P. (2015). Microglia recapitulate a hematopoietic master regulator network in the aging human frontal cortex. *Neurobiol Aging* 36, 2443.e2449-2443.e2420.

Wen, Y., Ouyang, Z., Devreese, B., He, W., Shao, Y., Lu, W., and Zheng, F. (2017). Crystal structure of master biofilm regulator CsgD regulatory domain reveals an atypical receiver domain. *Protein Sci* 26, 2073-2082.

Whyte, Warren A., Orlando, David A., Hnisz, D., Abraham, Brian J., Lin, Charles Y., Kagey, Michael H., Rahl, Peter B., Lee, Tong I., and Young, Richard A. (2013). Master Transcription Factors and Mediator Establish Super-Enhancers at Key Cell Identity Genes. *Cell* 153, 307-319.

Witczak, C.A., Sharoff, C.G., and Goodyear, L.J. (2008). AMP-activated protein kinase in skeletal muscle: From structure and localization to its role as a master regulator of cellular metabolism. *Cellular and Molecular Life Sciences* 65, 3737-3755.

Wolański, M., Jakimowicz, D., and Zakrzewska-Czerwińska, J. (2014). Fifty years after the replicon hypothesis: cell-specific master regulators as new players in chromosome replication control. *Journal of bacteriology* 196, 2901-2911.

Xia, P., and Xu, X.-Y. (2015). PI3K/Akt/mTOR signaling pathway in cancer stem cells: from basic research to clinical application. *Am J Cancer Res* 5, 1602-1609.

Yang, H., Liang, H., Yan, J.-s., Tao, R., Hao, S.-g., and Ma, L.-y. (2012). Down-regulation of hematopoiesis master regulator PU.1 via aberrant methylation in chronic myeloid leukemia. *International Journal of Hematology* 96, 65-73.

Yang, Z., Rayala, S., Nguyen, D., Vadlamudi, R.K., Chen, S., and Kumar, R. (2005). Pak1 Phosphorylation of Snail, a Master Regulator of Epithelial-to-Mesenchyme Transition, Modulates Snail's Subcellular Localization and Functions. *Cancer Research* 65, 3179-3184.

Yu, X., Ng, C.P., Habacher, H., and Roy, S. (2008). Foxj1 transcription factors are master regulators of the motile ciliogenic program. *Nature Genetics* 40, 1445-1453.

Zeng, H. (2017). mTOR signaling in immune cells and its implications for cancer immunotherapy. *Cancer Letters* 408, 182-189.

Zhang, M.-l., Nie, F.-q., Sun, M., Xia, R., Xie, M., Lu, K.-h., and Li, W. (2015). HOXA5 indicates poor prognosis and suppresses cell proliferation by regulating p21 expression in non small cell lung cancer. *Tumor Biology* 36, 3521-3531.

Zhang, S., Zhang, T., Yan, M., Ding, J., and Chen, J. (2014). Crystal structure of the WOPR-DNA complex and implications for Wor1 function in white-opaque switching of *Candida albicans*. *Cell research* 24, 1108-1120.

Zona, S., Bella, L., Burton, M.J., Nestal de Moraes, G., and Lam, E.W.F. (2014). FOXM1: an emerging master regulator of DNA damage response and genotoxic agent resistance. *Biochim Biophys Acta* 1839, 1316-1322.

**Table 1** (on next page)

Summary of master regulator family and related functions



1 Table 1. Summary of master regulator family and related functions

Family master regulator gene	Members	functions
CDX Family	all	master regulator of HOX family gene (Frohling, et al. 2007; Rawat, et al. 2012; Shiotani, et al. 2008)
CDK Family	CDK1、CDK2、Cdc5	master regulator of cell cycle regulation (Botchkarev and Haber 2018; Hinds 2003; Satyanarayana and Kaldis 2009)
HSFs Family	HSF1、HSF2、HSFA1	master regulator of heat shock reaction (Filone, et al. 2014; Liu and Charng 2012; Qiao, et al. 2017; Shinkawa, et al. 2011)
MTA Family	all	master regulator of the occurrence and metastasis of cancer (Du, et al. 2017; Li, et al. 2009; P 2014)
SREBP Family	all	master regulator of lipid homeostasis (Gong, et al. 2016; Krycer, et al. 2010; Madison 2016)
Rho Family	Including RhoA, Rac1 and Cdc42 proteins, and so on	master regulator for a large number of cell functions, including control of cell morphology, cell migration and polarity, transcriptional activation and cell cycle progression (Bai, et al. 2015; Colomba and Ridley 2014; Costa, et al. 2011; P 2014; Singh, et al. 2019; Watanabe, et al. 2006; Zago, et al. 2019)
HNF (Hepatocyte nuclear factor) Family	Including HNF1A/B、HNF4alpha、HNF6	master regulator of pancreas and liver differentiation (Alder, et al. 2014; Janky, et al. 2016; Kondratyeva, et al. 2017; Odom, et al. 2004; Sandovici, et al. 2013)
IL(interleukin) Family	Including IL-1、IL-2、IL-6、IL-7、IL-10、IL-12、IL-21、IL-23、IL-27, and so on	master regulator of inflammation or immunity (Fry and Mackall 2001; Langrish, et al. 2004; Neurath 2007; Qin, et al. 2017; Rojas, et al. 2017; Sharma, et al. 2011; Waldner and Neurath 2014; Wilson and Esposito 2009)

Rab Superfamily	GTPases	Including Rab5, Rab7b, Rab11 GTPase, and so on	master regulator of cell membrane transport (Distefano, et al. 2015; Ishida, et al. 2016; Pfeffer 2017; Qi, et al. 2015; Wu, et al. 2015)
The MiTF/TFE Family of Transcription Factors	MITF, TFEB, TFE3, TFEC		Master Regulators of Organelle Signaling, Metabolism, and Stress Adaptation (Slade and Pulinilkunnil 2017)
	all		master regulator of cell division
PLK Family	PLK1		master regulator of mitotic related kinases (Combes, et al. 2017)
	PLK4		master regulator of the formation of centrioles (Levine and Holland 2014; Shaheen, et al. 2014)
	all		master regulator of development and tissue homeostasis (Relaix 2015)
PAX Family	Pax5		master regulator of b-cell development and leukemia (Medvedovic, et al. 2011; Nebral, et al. 2009)
	Pax6		master regulator of nerve and eye development (Albert, et al. 2013; Shubham and Mishra 2012)
	TBX1		master regulator of muscle differentiation (Chen, et al. 2009)
TBX Family	TBX5		master regulator of heart development (Boogerd and Evans 2016)
	TBX21		master regulator of Th1 cell development (Nicol, et al. 2016b; Stolarczyk, et al. 2014; Wilkie, et al. 2016)
	SOX2		master regulator of mammalian embryogenesis, embryonic stem cell self-renewal and pluripotency (Rizzino 2008; Whyte, et al. 2013)
	SOX3		master regulator of innate immunity (Doostparast Torshizi and Wang 2017)
SOX Family	SOX4		master regulator of EMT(epithelial-mesenchymal transition) (Lourenço and Coffe 2017; Tiwari, et al. 2013)

	Sox5、Sox6	the interaction with SOX9 is a master regulator of cartilage development (Ma, et al. 2016; Suzuki, et al. 2012; Vivekanandan, et al. 2015)
		master regulator of testis differentiation pathway (Jakob and Lovell-Badge 2011; Mork and Capel 2010; VG 2012)
	SOX9	master regulator of fibroblast differentiation (Noizet, et al. 2016) master regulator of pancreatic program (Julian, et al. 2017; Seymour 2014)
RUNX Family	SOXB1、SOXE、SOXF	master regulator of cell fate (Julian, et al. 2017)
	RUNX1	master regulator of adult hematopoiesis (Ichikawa, et al. 2004; Wehrspaun, et al. 2015; Wu, et al. 2014)
	RUNX2	master regulator of osteoblast lineage (Liu, et al. 2017; Wysokinski, et al. 2015)
IRF Family	IRF-1	master regulator of cross talk between macrophage and L929 fibrosarcoma cells (Nascimento, et al. 2015)
	IRF4	master regulator of human periodontitis (Sawle, et al. 2016)
	IRF7	master regulator of IFN-I, virus-induced cytokine (Hu, et al. 2011; Lu, et al. 2015; Wang, et al. 2013)
Bcl Family	IRF8	master regulator of monocytes and dendritic cells development (T 2017b)
	Bcl-2	master regulator of apoptosis (Chen, et al. 2012; Häcker and Vaux 1995)
	Bcl-6	master regulator of Tfh cell differentiation (Matsumoto, et al. 2017)
C/EBP Family	BCL11B	master regulator of t cell (Th) differentiation (Inoue, et al. 2016)
	Bcl2l10	master regulator of Aurora kinase a mouse oocytes (Lee, et al. 2016)
	C/EBPα	master regulator of the bone marrow progenitor cells and fat

formation (Ding, et al. 2011; Okuno, et al. 2013)

master regulator of physiological cardiac hypertrophy (Molkentin

C/EBPbeta

Jeffery 2011)

2

3

# **Table 2**(on next page)

Summary of the MRGs involved in important signaling pathways

1 Table 2. Summary of the MRGs involved in important signaling pathways

Signaling pathway	master regulator		functions
	gene		
TGF- $\beta$ signaling pathway	whole pathway	signal	master regulator of the respiratory system, epithelial-mesenchymal transition and metastasis, and cancer development, etc (Fazilaty, et al. 2013; Solomon, et al. 2010; Zhou, et al. 2014)
PI3K-AKT-mTOR signaling pathway	whole pathway	signal	master regulator of cancer (Xia and Xu 2015)
Hedgehog (Hh) signaling pathway	whole pathway	signal	master regulator of cell differentiation (Peng and Joyner 2015)
NF-kappaB signaling pathway	whole pathway	signal	master regulator of innate immunity and inflammatory signaling (Krappmann, et al. 2004; Matroule, et al. 2006; Zeitz, et al. 2017)
Wnt signaling pathway	whole pathway	signal	master regulator of cell development and cell polarization (Gómez-Orte, et al. 2013)
	Wnt5a		master regulator of brain invasion (Binda, et al. 2017)
	Wnt / $\beta$ -catenin		master regulator of the liver region and multiple RAS (renin-angiotensin system) genes (Torre, et al. 2010)
Notch signaling pathway	Notch		The fate of arteriovenous-lymphatic endothelial cells is regulated by the master regulator of Notch, COUP-TFII, and Prox1 (Kang, et al. 2010)
	Notch3		master regulator of neuroblastoma movement (van Nes, et al. 2013)
Yap signaling pathway	Yap1		master regulator of endometriosis (Lin, et al. 2017b)
Hypoxia signaling pathway	HIF-1 $\alpha$		master regulators of the adaptive response to hypoxia

HIF-2  $\alpha$  (Lu and Kang 2010; Schönenberger and Kovacs  
2015; Xiao 2015)

---

2

3

# **Table 3**(on next page)

Summary of master regulator genes related to heart disease



1 Table 3. Summary of master regulator genes related to heart disease

Master regulator genes	Cardiovascular disease type
TBX5、NuRD	Congenital heart disease (Boogerd and Evans 2016)
SREBP	Treatment of cardiac metabolic diseases (Krycer, et al. 2010)
VEGF	Vascular disease (Danese 2008; Gianni-Barrera, et al. 2014)
MyoD	Heart disease (Kojima and Ieda 2017)
PPAR $\gamma$	Obesity, diabetes and cardiovascular disease (Lee and Ge 2014; Lehrke and Lazar 2005)
PKC $\delta$	Thrombosis complications (Fischer 2009)
SCL/TAL1	Anemia patient (T 2017)
Class IB phosphoinositide 3-kinase p110s	Heart disease (Perino, et al. 2010)
PI3K	Heart failure (Weeks KL1 2012 )
SOX9 and myocardin	Atherosclerosis, vascular calcification (Xu, et al. 2012)
Klotho	Cardiovascular diseases (Moe Sharon 2012)
PITX2	Atrial fibrillation (AF) is the most common persistent Arrhythmia (Li, et al. 2016)
FLYWCH1, PSORSIC3, G3BP1	Coronary artery disease(CAD) (Foroughi Asl, et al. 2015)
Thyroid hormones (THs)	Cardiovascular diseases (Rajagopalan and Gerdes 2015)
CST	Cardiovascular diseases(CVD) (Sushil, et al. 2018)
Etv2	Chronic vascular disease (Garry 2016)

2

3