Hypoxia inducible factor in nephrotoxicity

Subjects: Oncology

Contributor: Zheng Dong

Cisplatin is a highly effective, broad-spectrum chemotherapeutic drug, yet its clinical use and efficacy are limited by its side effects. Particularly, cancer patients receiving cisplatin chemotherapy have high incidence of kidney problems. Hypoxia-inducible factor (HIF) is the “master” transcription factor that is induced under hypoxia to trans-activate various genes for adaptation to the low oxygen condition. Numerous studies have reported that HIF activation protects against AKI and promotes kidney recovery in experimental models of cisplatin-induced acute kidney injury (AKI). In contrast, little is known about the effects of HIF on chronic kidney problems following cisplatin chemotherapy. Prolyl hydroxylase (PHD) inhibitors are potent HIF inducers that recently entered clinical use. By inducing HIF, PHD inhibitors may protect kidneys during cisplatin chemotherapy. However, HIF activation by PHD inhibitors may reduce the anti-cancer effect of cisplatin in tumors.

Keywords: cisplatin ; HIF ; hypoxia ; acute kidney injury ; chronic kidney disease

1. Introduction

Cisplatin is an effective and broad-spectrum chemotherapeutic agent for various kind of tumors. Though being used worldwide, the therapeutic efficacy of cisplatin is limited, to some extent, by its side effects in normal tissues including ototoxicity, neurotoxicity, and nephrotoxicity[1]. Among them, cisplatin-induced kidney injury or nephrotoxicity is life-threatening and has attracted great attention with numerous studies focusing on its underlying mechanisms and potential therapeutic strategies[2][3]. Cisplatin can induce both acute kidney injury (AKI)[3][4] and the chronic kidney diseases (CKD) following AKI[5][6][7].

Hypoxia is a common factor involved in the development of renal pathology in both AKI and CKD [10]. Hypoxia-inducible factor(HIF) is generally considered as the core regulator for maintaining oxygen homeostasis due to its crucial role in cellular sensing and adaption to hypoxia[8][9][10]. As a transcription factor, HIF binds to DNA in a sequence-specific manner to promote or repress the transcription of multiple genes. HIF is widely involved in various biological processes, such as oxygen sensing, angiogenesis, vasodilation, erythropoiesis, metabolism, inflammation, and cell-cycle regulation[11][12]. Several studies have reported that HIF may participate in cisplatin-induced nephrotoxicity. However, most of these studies focus on cisplatin-induced AKI and find that HIF activation may protect against tubular cell injury and promote kidney recovery[13][14][15][16]. The lack of information of HIF in AKI to CKD progression and chronic kidney problems following cisplatin exposure make it an urgent need to study the regulation of HIF in these conditions.

Hypoxia is a known condition in solid tumors due to abnormal cancer cellular proliferation, expansion of tumor size and disruption of angiogenesis. As such, HIF is activated in tumors for cellular adaptation, and studies have found that inhibition of HIF may be an anti-cancer strategy under some circumstances [17]. In cisplatin chemotherapy, the activation of HIF for kidney protection may therefore antagonize the anti-tumor effects. Thus, when considering HIF activation as a kidney-protective strategy in cisplatin chemotherapy, the effect on cisplatin's anti-tumor efficiency has to be taken into consideration.

2. HIF in Cisplatin-Induced AKI

Over the past few decades, several studies demonstrated the evidence for a reno-protective role of HIF in cisplatin-induced AKI. These studies are summarized in Table 1.

Table 1. Summary of studies about the role of HIF in cisplatin-induced AKI.

Number	Model	Strategies for HIF Regulation	Involved HIF Isoforms	Is HIF Activated or Inhibited	Effects	Underlying Mechanisms	Reference
1	Rats	cobalt	HIF-1 and HIF-2,	activated	attenuate AKI	apoptosis reduction via regulating mitochondrial pathways	[14]
	IRPTC,		HIF-1	activated	improve IRPTC survival		
2	Rats;	Carbon monoxide preconditioning	HIF-1	activated	attenuated AKI	apoptosis reduction	[16]
	HCK-8 cells		HIF-1	activated	reduced apoptosis, increased proliferation		
3	Mice;	PHD inhibitor FG-4592	HIF-1	activated	attenuated AKI	apoptosis reduction, ameliorated inflammation	[15]
	HK-2 cells		HIF-1	activated	reduced apoptosis		
4	Rats	deferiprone	HIF-1	activated	attenuated AKI	reduce apoptosis with increased Mcl1 and survivin expression	[13]
5	Mice	EC-specific Phd2+/- mice	HIF-1, HIF-2	activated	attenuated AKI	induced antioxidative response	[18]
6	HK-2 cells	lentivirus-mediated HIF-1α-transfected hASCs	HIF-1	activated	reduced apoptosis and improved cellular morphology	reduced apoptosis	[19]
7	Mice	lentivirus-mediated HIF-1α-transfected hASCs	HIF-1	activated	attenuated AKI	reduced apoptosis, ameliorated inflammation	[20]

IRPTC, immortalized rat proximal tubular cells; HCK-8, human renal proximal tubular cell line; HK-2, human proximal tubule epithelial cells; Mcl1, Myeloid cell leukemia-1; EC, endothelial cell; hASCs, Human adipose-derived stem cells.

HIF induction in cisplatin-induced AKI has been reported by several studies though whether cisplatin can directly activate HIF is still controversial. It is possible that in in vitro conditions, the existence of normal oxygen (21% O_2 level usually used for cell cultivation) may prevent HIF activation with cisplatin injury. However, in in vivo conditions, cisplatin-induced vascular damage and renal blood flow reduction may break the balance between low delivery and high consumption of oxygen in renal tubules, leading to severe local hypoxia[21]. Though with some variations in different in vivo models, HIF is likely activated due to this local hypoxia after cisplatin injury.

Consistently, the protective effect of HIF activation has been reported in several studies , The in vivo and in vitro evidence implicates that HIF up-regulation can be an effective therapeutic strategy for preventing cisplatin-induced AKI. [13][14][15][16][18][19][20]. Currently, the underlying mechanism for the reno-protection of HIF in cisplatin induced nephrotoxicity has been explored but not completely understood (Figure 2). In most of the studies, the reduction of renal tubular apoptosis has been reported[13]. In addition, HIF activation is also associated with anti-oxidative effects, showing less lipid peroxidation[18], which may be related to ferroptosis inhibition. Furthermore, HIF activation may protect endothelial cells because angiogenesis-related genes such as VEGF may be induced[19][20]. The anti-inflammation effect of HIF activation may also contribute to its reno-protection. HIF upregulation by PHD inhibitor or HIF-1α overexpression can significantly reduce multiple cytokine release after cisplatin injury, which can lead to less inflammatory cell infiltration and reduced renal injury[15][20]. Finally, HIF also interacts with other pathways that are involved in the development and progress of cisplatin-induced AKI, like cell cycle arrest, autophagy. In conclusion, current evidence indicates that HIF activation is beneficial to the kidney during cisplatin chemotherapy. Further investigation on HIF-1 and its interaction with other cellular process may reveal deeper understanding and novel therapeutic targets of cisplatin-induced AKI.

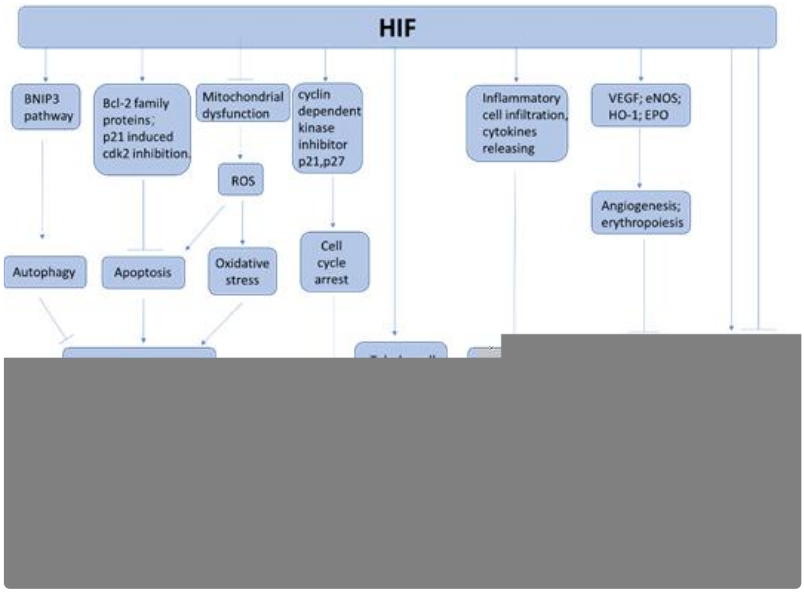

Figure 2. The involvement of HIF in cisplatin-induced nephrotoxicity. During cisplatin chemotherapy, HIF may protect kidneys from AKI and CKD by the inhibition of tubular cell death, the regulation of cell proliferation, the suppression of kidney inflammation, and the attenuation of vascular damage.

3.HIF in Cisplatin-Induced AKI to CKD Progression

Numerous evidences have demonstrated that tubulointerstitial hypoxia is not only an essential contributor to AKI but also a key player in CKD. Chronic hypoxia is considered as a common pathological condition in CKD[22][23]. Though studies have revealed that multiple pathophysiological mechanisms are related to cisplatin-induced AKI to CKD progression [7][24][25][26][27][28], the investigation focusing on the role of HIF in this field is lacking. Nevertheless, HIF is a potential player in this process because of its essential role in hypoxia and its interactions with multiple pathophysiological procedures involved in the progression of CKD such as as tubular cell proliferation, oxidative stress, inflammation and interstitial fibrosis (Figure 2).

4.Therapeutic Potential of HIF in Cisplatin Chemotherapy

In view of the role of HIF in cisplatin-induced nephrotoxicity, targeting or activating HIF and its related pathways may be a therapeutic strategy. PHD-pVHL pathway plays a vital role in HIF regulation, and pharmacological or genetic inhibition of PHD activity is under intensive research in kidney diseases[15][29][30][31][32][33][34][35][36][18,45,167,168,181–185]. The role of regulating HIF in cisplatin-induced nephrotoxicity is summarized in Table 1; besides the evidence that HIF accumulation

by PHD inhibitors treatment protects against cisplatin-induced nephrotoxicity [[15]], studies have reported beneficial effects of PHD inhibitors in other kidney diseases including ischemic AKI[30][31], diabetic nephropathy[33][34], obesity related kidney disease[32], chronic tubulointerstitial nephritis[35], and remnant kidneys models of CKD[37]. A great breakthrough in this field is that PHD inhibitors have been proved to have a therapeutic effect in anemia, a complication of CKD that contributes to poor clinical outcome[38].

Notably, although HIF activation may have protective effect on kidney during cisplatin chemotherapy, it may attenuate the anti-cancer effects of cisplatin in tumors [195]. Studies have revealed HIF overexpression in multiple tumors [17][39] and found that HIF is closely related to tumor resistance to cisplatin[40][41][42][43]. More studies showing HIF's involvement in cancers during cisplatin chemotherapy are summarized in Table 2. In general, inhibiting HIF has been shown as a powerful strategy to reinforce anti-cancer efficiency of chemotherapeutic strategies including cisplatin [44][45][46][47]. Thus, in cisplatin chemotherapy, activating HIF is a double-edged sword. The failure to balance its effects on cisplatin's anti-tumor function and nephrotoxicity may limit its application in cisplatin-induced AKI or CKD. Therefore, the clinical application of PHD inhibitors to reduce the side-effect of cisplatin requires further investigation and evaluation.

In conclusion, when considering therapeutic strategies activating or targeting HIF in cisplatin-induced nephrotoxicity, more comprehensive and rigorous work is still needed to identify novel chemicals or drug delivery techniques to achieve the maximal reno-protective effect without diminishing the anti-tumor efficacy of cisplatin.

Table 2. Summary of studies about therapeutic potential of HIF in cisplatin chemotherapy.

Number	Model	Strategies for HIF Regulation	Involved HIF Isoforms	Is HIF Activated or Inhibited	Effects	Underlying Mechanisms	Reference
1	Ovarian cancer cell lines	HIF-1α SiRNA; 1-methyl-1, 9 PA	HIF-1α	inhibited	increased cancer cell sensitivity to cisplatin	Regulation of aerobic glycolysis and mitochondrial oxidative phosphorylation; induced apoptosis through ROS overproduction	[43]
2	Ovarian cancer cell lines	HIF-1α SiRNA	HIF-1α	inhibited	increased cancer cell sensitivity to cisplatin	Regulation of the interaction between p53 and RAS signaling and dysregulation of apoptosis and autophagy	[42]
	mice with ovarian cancer cell tumor xenograft			inhibited	inhibited tumor growth		
3	Ovarian cancer cell lines	Topotecan	HIF-1α	inhibited	reversed hypoxia-induced cisplatin and paclitaxel resistance	restored p53 transcriptional activity, downregulated ABCB1/ABCB5 cell surface expression	[48]

4	Lung adenocarci-noma Cells	HIF-2α SiRNA	HIF-2α	inhibited	increased cancer cell sensitivity to cisplatin	decreased the expression of P-glycoprotein 1	[49]
5	Human lung adenocarci-noma cell lines	HIF-1α SiRNA	HIF-1α	inhibited	increased cancer cell sensitivity to cisplatin	decreased MDR1 and MRP expression	[50]
6	Human lung adenocarci-noma cell lines	HIF-1α SiRNA	HIF-1α	inhibited	increased cancer cell sensitivity to cisplatin	Unsure, possibly related to mechanisms other than MDR1 gene regulation	[51]
7	mice with tumor xenograft from human ESCC cell	HIF-1α SiRNA	HIF-1α	inhibited	inhibited tumor growth	induced cell apoptosis	[52]
8	Human NSCLC cell lines	Panobinost-at	HIF-1α	inhibited	inhibited cell proliferation and viability; suppressed growth of multicellular spheroids	More chromatin fragmentation and induction of apoptosis	[53]
9	Human prostate cancer cell mice with tumor xenograft from human prostate cancer cell	HIF-1α SiRNA	HIF-1α	inhibited	inhibited cell viability, proliferation, and colony formation capability inhibited tumor growth	induced apoptosis through ROS overproduction	[54]
10	Human NSCLC cell lines mice with tumor xenograft from human NSCLC cell	Oroxylin A	HIF-1α	inhibited	increased cancer cell sensitivity to cisplatin reduced tumor growth	inhibited nucleotide excision repair through suppressing XPC transcription	[55]

11	Human ovarian cancer line	Noscapine	HIF-1α	inhibited	increased cancer cell sensitivity to cisplatin	downregulated HIF-1 transcriptional activity and MDR1 overexpression	[56]
12	Human NPC cell lines	Evofosfami-de	HIF-1α	inhibited	exhibited hypoxia-selective cytotoxicity and increased cancer cell sensitivity to cisplatin	induced G2 cell cycle arrest and DNA damage	[57].
	Tumor-bearing mice with xenograft derived from human NPC cell lines				inhibited tumor growth		
13	Chondrosarcoma cell lines	EPAS1 shRNA	HIF-2α	inhibited	decreased sphere-forming potential, clonogenicity, and proliferative capacity; suppressed cell invasiveness	induced cell apoptosis	[58]
	Chondrosarcoma cell lines	HIF-2α inhibitor TC-S7009			blocked sphere formation, clonogenicity, invasive phenotypes, and matrix-degrading activity		
	Tumor-bearing mice with xenograft derived from chondrosarcoma cell lines				nearly abolished invasive outgrowth and profound suppression of metastasis		

					normalized tumor		
14	Tumor-bearing mice with xenograft derived from melanoma cells	EC-specific Phd2+/- mice	HIF-1, HIF-2	activated	vessels; inhibited tumor growth, increased tumor sensitivity to cisplatin	increased vessel perfusion and drug delivery.	[18]

1-methyl-1, 9 PA, 1-methyl-1, 9-pyrazoloanthrone; ABCB1, ATP Binding Cassette Subfamily B Member 1; ABCB5, ATP Binding Cassette Subfamily B Member 5; MDR1, multidrug resistance-1; MRP, multidrug resistance-associated protein; ESCC, esophagus squamous cell carcinoma; NPC, nasopharyngeal carcinoma; EPAS1, Endothelial PAS Domain Protein 1.

References

1. Takatoshi Karasawa; Peter S. Steyger; An integrated view of cisplatin-induced nephrotoxicity and ototoxicity. *Toxicology Letters* **2015**, *237*, 219-227, 10.1016/j.toxlet.2015.06.012.
2. Hamroun, A; Prevention of Cisplatin-Induced Acute Kidney Injury: A Systematic Review and Meta-Analysis. *Drugs* **2019**, *79*, 1567–1582, .
3. Sandhya Manohar; Nelson Leung; Cisplatin nephrotoxicity: a review of the literature. *Journal of Nephrology* **2017**, *31*, 15-25, 10.1007/s40620-017-0392-z.
4. N. Pabla; Zheng Dong; Cisplatin nephrotoxicity: Mechanisms and renoprotective strategies. *Kidney International* **2008**, *73*, 994-1007, 10.1038/sj.ki.5002786.
5. Mingjun Shi; Kathryn L. McMillan; Junxia Wu; Nancy Gillings; Brianna Flores; Orson W. Moe; Ming Chang Hu; Cisplatin nephrotoxicity as a model of chronic kidney disease. *Laboratory Investigation* **2018**, *98*, 1105-1121, 10.1038/s41374-018-0063-2.
6. Sarah I. Landau; Xiaojia Guo; Heino Velazquez; Richard Torres; Eben Olson; Rolando Garcia-Milian; Gilbert W. Moeckel; Gary V. Desir; Robert Safirstein; Regulated necrosis and failed repair in cisplatin-induced chronic kidney disease. *Kidney International* **2019**, *95*, 797-814, 10.1016/j.kint.2018.11.042.
7. Ying Fu; Juan Cai; FangHua Li; Zhiwen Liu; Shaoqun Shu; Ying Wang; Yuxue Liu; Chengyuan Tang; Zheng Dong; Chronic effects of repeated low-dose cisplatin treatment in mouse kidneys and renal tubular cells. *American Journal of Physiology-Renal Physiology* **2019**, *317*, F1582-F1592, 10.1152/ajprenal.00385.2019.
8. G L Semenza; G L Wang; A nuclear factor induced by hypoxia via de novo protein synthesis binds to the human erythropoietin gene enhancer at a site required for transcriptional activation.. *Molecular and Cellular Biology* **1992**, *12*, 5447-5454, 10.1128/mcb.12.12.5447.
9. Guang L. Wang; Gregg L. Semenza; Purification and Characterization of Hypoxia-inducible Factor 1. *Journal of Biological Chemistry* **1994**, *270*, 1230-1237, 10.1074/jbc.270.3.1230.
10. Gregg L. Semenza; Oxygen homeostasis. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine* **2010**, *2*, 336-361, 10.1002/wsbm.69.
11. Frank J. Gonzalez; Cen Xie; Changtao Jiang; The role of hypoxia-inducible factors in metabolic diseases. *Nature Reviews Endocrinology* **2018**, *15*, 21-32, 10.1038/s41574-018-0096-z.
12. Gregg L. Semenza; Hypoxia-Inducible Factors in Physiology and Medicine. *Cell* **2012**, *148*, 399-408, 10.1016/j.cell.2012.01.021.
13. Pouran Makhdoumi; Khalil Abnous; Soghra Mehri; Leila Etemad; Mohsen Imenshahidi; Gholamreza Karimi; Oral deferiprone administration ameliorates cisplatin-induced nephrotoxicity in rats. *Journal of Pharmacy and Pharmacology*

2018, *70*, 1357-1368, 10.1111/jphp.12990.

14. Tetsuhiro Tanaka; Ichiro Kojima; Takamoto Ohse; Reiko Inagi; Toshio Miyata; Julie R. Ingelfinger; Toshiro Fujita; Masaomi Nangaku; Hypoxia-inducible factor modulates tubular cell survival in cisplatin nephrotoxicity. *American Journal of Physiology-Renal Physiology* **2005**, *289*, F1123-F1133, 10.1152/ajprenal.00081.2005.

15. Yunwen Yang; Xiaowen Yu; Yue Zhang; Guixia Ding; Chunhua Zhu; Songming Huang; Zhanjun Jia; Aihua Zhang; Hypoxia-inducible factor prolyl hydroxylase inhibitor roxadustat (FG-4592) protects against cisplatin-induced acute kidney injury. *Clinical Science* **2018**, *132*, 825-838, 10.1042/cs20171625.

16. Alexander Weidemann; Wanja M. Bernhardt; Bernd Klanke; Christoph Daniel; Björn Buchholz; Valentina Câmpean; Kerstin Amann; Christina Warnecke; Michael S. Wiesener; Kai-Uwe Eckardt; et al. HIF Activation Protects From Acute Kidney Injury. *Journal of the American Society of Nephrology* **2008**, *19*, 486-494, 10.1681/asn.2007040419.

17. Gregg L. Semenza; Targeting HIF-1 for cancer therapy. *Nature Cancer* **2003**, *3*, 721-732, 10.1038/nrc1187.

18. Rodrigo Leite De Oliveira; Sofie Deschoemaeker; Anne-Theres Henze; Koen DeBackere; Veronica Finisguerra; Yukiji Takeda; Carmen Roncal; Daniela Dettori; Evelyne Tack; Yannick Jönsson; et al. Gene-Targeting of Phd2 Improves Tumor Response to Chemotherapy and Prevents Side-Toxicity. *Cancer Cell* **2012**, *22*, 263-277, 10.1016/j.ccr.2012.06.028.

19. Weiwei Wang; Wei Wang; Yan Jiang; Zezheng Li; Jin Cheng; Nanmei Liu; Guofeng Han; Shi Lu; Jinyuan Zhang; Human adipose-derived stem cells modified by HIF-1α accelerate the recovery of cisplatin-induced acute renal injury in vitro. *Biotechnology Letters* **2013**, *36*, 667-676, 10.1007/s10529-013-1389-x.

20. Wei-Wei Wang; Ze-Zheng Li; Yan Jiang; Jin Cheng; Shi Lu; Jinyuan Zhang; Wei Wang; Enhanced renoprotective effect of HIF-1α modified human adipose-derived stem cells on cisplatin-induced acute kidney injury in vivo. *Scientific Reports* **2015**, *5*, 10851, 10.1038/srep10851.

21. J. A. Winston; R. Safirstein; Reduced renal blood flow in early cisplatin-induced acute renal failure in the rat. *American Journal of Physiology-Renal Physiology* **1985**, *249*, F490-F496, 10.1152/ajprenal.1985.249.4.f490.

22. Shaoqun Shu; Ying Wang; Meiling Zheng; Zhiwen Liu; Juan Cai; Chengyuan Tang; Zheng Dong; Hypoxia and Hypoxia-Inducible Factors in Kidney Injury and Repair. *Cells* **2019**, *8*, 207, 10.3390/cells8030207.

23. Masaomi Nangaku; Chronic Hypoxia and Tubulointerstitial Injury: A Final Common Pathway to End-Stage Renal Failure. *Journal of the American Society of Nephrology* **2005**, *17*, 17-25, 10.1681/asn.2005070757.

24. Daisuke Katagiri; Yoshifumi Hamasaki; Kent Doi; Kousuke Negishi; Takeshi Sugaya; Masaomi Nangaku; Eisei Noiri; Interstitial renal fibrosis due to multiple cisplatin treatments is ameliorated by semicarbazide-sensitive amine oxidase inhibition. *Kidney International* **2016**, *89*, 374-385, 10.1038/ki.2015.327.

25. Anna Menshikh; Lauren Scarfe; Rachel Delgado; Charlene Finney; Yuantee Zhu; Haichun Yang; Mark P. De Caestecker; Capillary rarefaction is more closely associated with CKD progression after cisplatin, rhabdomyolysis, and ischemia-reperfusion-induced AKI than renal fibrosis. *American Journal of Physiology-Renal Physiology* **2019**, *317*, F1383-F1397, 10.1152/ajprenal.00366.2019.

26. Kranti A. Mapuskar; Hsiang Wen; Danniele G. Holanda; Prerna Rastogi; Emily Steinbach; Rachel Han; Mitchell C. Coleman; Massimo Attanasio; Dennis P. Riley; Douglas R. Spitz; et al. Persistent increase in mitochondrial superoxide mediates cisplatin-induced chronic kidney disease. *Redox Biology* **2018**, *20*, 98-106, 10.1016/j.redox.2018.09.020.

27. Seiji Kishi; Craig R. Brooks; Kensei Taguchi; Takaharu Ichimura; Yutaro Mori; Akinwande Akinfolarin; Navin Gupta; Pierre Galichon; Bertha C. Elias; Tomohisa Suzuki; et al. Proximal tubule ATR regulates DNA repair to prevent maladaptive renal injury responses. *Journal of Clinical Investigation* **2019**, *129*, 4797-4816, 10.1172/jci122313.

28. Caizhen Li; Na Xie; Yan Li; Chongbin Liu; Fanfan Hou; Jun Wang; N-acetylcysteine ameliorates cisplatin-induced renal senescence and renal interstitial fibrosis through sirtuin1 activation and p53 deacetylation. *Free Radical Biology and Medicine* **2018**, *130*, 512-527, 10.1016/j.freeradbiomed.2018.11.006.

29. Patrick Henry Maxwell; Kai-Uwe Eckardt; HIF prolyl hydroxylase inhibitors for the treatment of renal anaemia and beyond. *Nature Reviews Nephrology* **2015**, *12*, 157-168, 10.1038/nrneph.2015.193.

30. Pinelopi P. Kapitsinou; Jonathan Jaffe; Mark Michael; Christina E. Swan; Kevin J. Duffy; Connie L. Erickson-Miller; Volker H. Haase; Preischemic targeting of HIF prolyl hydroxylation inhibits fibrosis associated with acute kidney injury. *American Journal of Physiology-Renal Physiology* **2012**, *302*, F1172-F1179, 10.1152/ajprenal.00667.2011.

31. Pinelopi P. Kapitsinou; Hideto Sano; Mark Michael; Hanako Kobayashi; Olena Davidoff; Aihua Bian; Bing Yao; Ming-Zhi Zhang; Raymond C. Harris; Kevin J. Duffy; et al. Endothelial HIF-2 mediates protection and recovery from ischemic kidney injury. *Journal of Clinical Investigation* **2014**, *124*, 2396-2409, 10.1172/jci69073.

32. Hisako Saito; Tetsuhiro Tanaka; Mai Sugahara; Shinji Tanaka; Kenji Fukui; Takeshi Wakashima; Masaomi Nangaku; Inhibition of prolyl hydroxylase domain (PHD) by JTZ-951 reduces obesity-related diseases in the liver, white adipose

tissue, and kidney in mice with a high-fat diet. *Laboratory Investigation* **2019**, *99*, 1217-1232, 10.1038/s41374-019-0239-4.

33. Mai Sugahara; Shinji Tanaka; Tetsuhiro Tanaka; Hisako Saito; Yu Ishimoto; Takeshi Wakashima; Masatoshi Ueda; Kenji Fukui; Akira Shimizu; Reiko Inagi; et al. Prolyl Hydroxylase Domain Inhibitor Protects against Metabolic Disorders and Associated Kidney Disease in Obese Type 2 Diabetic Mice. *Journal of the American Society of Nephrology* **2020**, *31*, 560-577, 10.1681/asn.2019060582.

34. Sho Hasegawa; Tetsuhiro Tanaka; Tomoyuki Saito; Kenji Fukui; Takeshi Wakashima; Etsuo A. Susaki; Hiroki R. Ueda; Masaomi Nangaku; The oral hypoxia-inducible factor prolyl hydroxylase inhibitor enarodustat counteracts alterations in renal energy metabolism in the early stages of diabetic kidney disease. *Kidney International* **2020**, *97*, 934-950, 10.1016/j.kint.2019.12.007.

35. Gunnar Schley; Bernd Klanke; Joanna Kalucka; Valentin Schatz; Christoph Daniel; Marleen Mayer; Margarete Goppelt-Struebe; Martin Herrmann; Margret Thorsteinsdottir; Runolfur Palsson; et al. Mononuclear phagocytes orchestrate prolyl hydroxylase inhibition-mediated renoprotection in chronic tubulointerstitial nephritis. *Kidney International* **2019**, *96*, 378-396, 10.1016/j.kint.2019.02.016.

36. Ganeshkumar Rajendran; Michael P. Schonfeld; Ratnakar Tiwari; Shengping Huang; Rafael Torosyan; Timothy Fields; Jihwan Park; Katalin Susztak; Pinelopi P. Kapitsinou; Inhibition of Endothelial PHD2 Suppresses Post-Ischemic Kidney Inflammation through Hypoxia-Inducible Factor-1. *Journal of the American Society of Nephrology* **2020**, *31*, 501-516, 10.1681/asn.2019050523.

37. Xiaofang Yu; Yi Fang; Hong Liu; Jiaming Zhu; Jianzhou Zou; Xunhui Xu; Suhua Jiang; Xiaoqiang Ding; The balance of beneficial and deleterious effects of hypoxia-inducible factor activation by prolyl hydroxylase inhibitor in rat remnant kidney depends on the timing of administration. *Nephrology Dialysis Transplantation* **2012**, *27*, 3110-3119, 10.1093/ndt/gfr754.

38. Amit Joharapurkar; Vrajesh Bhaskarbhai Pandya; Vishal J. Patel; Ranjit C. Desai; Mukul R. Jain; Prolyl Hydroxylase Inhibitors: A Breakthrough in the Therapy of Anemia Associated with Chronic Disease. *Journal of Medicinal Chemistry* **2018**, *61*, 6964-6982, 10.1021/acs.jmedchem.7b01686.

39. H Zhong; A M De Marzo; E Laughner; M Lim; D A Hilton; D Zagzag; P Buechler; W B Isaacs; G L Semenza; J W Simons; et al. Overexpression of hypoxia-inducible factor 1alpha in common human cancers and their metastases.. *Cancer Research* **1999**, *59*, 5830–5835, .

40. Yi Sun; Zhenfeng Guan; Liang Liang; Yongyi Cheng; Jiancheng Zhou; Jing Li; Yonggang Xu; HIF-1α/MDR1 pathway confers chemoresistance to cisplatin in bladder cancer. *Oncology Reports* **2015**, *35*, 1549-1556, 10.3892/or.2015.4536.

41. Christophe Deben; Vanessa Deschoolmeester; Jorrit De Waele; Julie Jacobs; Jolien Van Den Bossche; An Wouters; Marc Peeters; Christian Rolfo; Evelien Smits; Filip Lardon; et al. Hypoxia-Induced Cisplatin Resistance in Non-Small Cell Lung Cancer Cells Is Mediated by HIF-1α and Mutant p53 and Can Be Overcome by Induction of Oxidative Stress. *Cancers* **2018**, *10*, 126, 10.3390/cancers10040126.

42. Xiaofei Zhang; Zihao Qi; Huijing Yin; Gong Yang; Interaction between p53 and Ras signaling controls cisplatin resistance via HDAC4- and HIF-1α-mediated regulation of apoptosis and autophagy. *Theranostics* **2018**, *9*, 1096-1114, 10.7150/thno.29673.

43. Zhihong Ai; Yang Lu; Songbo Qiu; Zhen Fan; Overcoming cisplatin resistance of ovarian cancer cells by targeting HIF-1-regulated cancer metabolism. *Cancer Letters* **2016**, *373*, 36-44, 10.1016/j.canlet.2016.01.009.

44. Gregg L. Semenza; Hypoxia-inducible factors: mediators of cancer progression and targets for cancer therapy. *Trends in Pharmacological Sciences* **2012**, *33*, 207-214, 10.1016/j.tips.2012.01.005.

45. Luana Schito; Gregg L. Semenza; Hypoxia-Inducible Factors: Master Regulators of Cancer Progression. *Trends in Cancer* **2016**, *2*, 758-770, 10.1016/j.trecan.2016.10.016.

46. Jaleh Fallah; Brian I. Rini; HIF Inhibitors: Status of Current Clinical Development. *Current Oncology Reports* **2019**, *21*, 6, 10.1007/s11912-019-0752-z.

47. Imran Hussain; Sana Waheed; Kashif A. Ahmad; John E. Pirog; Viqar Syed; Scutellaria baicalensistargets the hypoxia-inducible factor-1α and enhances cisplatin efficacy in ovarian cancer. *Journal of Cellular Biochemistry* **2018**, *119*, 7515-7524, 10.1002/jcb.27063.

48. Basmina Parmakhtiar; Robert A. Burger; Jai-Hyun Kim; John P. Fruehauf; HIF Inactivation of p53 in Ovarian Cancer Can Be Reversed by Topotecan, Restoring Cisplatin and Paclitaxel Sensitivity. *Molecular Cancer Research* **2019**, *17*, 1675-1686, 10.1158/1541-7786.mcr-18-1109.

49. Zhao-Jia Gao; Wei-Dong Yuan; Jun-Qiang Yuan; Kai Yuan; Yong Wang; Downregulation of HIF-2α Reverse the Chemotherapy Resistance of Lung Adenocarcinoma A549 Cells to Cisplatin. *Medical Science Monitor* **2018**, *24*, 1104-1111, 10.12659/msm.906107.

50. Shu-Ya He; Lingfeng Min; Qiong Chen; Shenggang Liu; Yun Ma; Hypoxia-induced increases in A549/CDDP cell drug resistance are reversed by RNA interference of HIF-1? expression. *Molecular Medicine Reports* **2011**, *5*, 228-232, 10.3892/mmr.2011.604.
51. Xianrang Song; Xianxi Liu; Weiling Chi; Yonglei Liu; Ling Wei; Xingwu Wang; Jinming Yu; Hypoxia-induced resistance to cisplatin and doxorubicin in non-small cell lung cancer is inhibited by silencing of HIF-1α gene. *Cancer Chemotherapy and Pharmacology* **2006**, *58*, 776-784, 10.1007/s00280-006-0224-7.
52. Hong-Ying Liao; Gui-Ping Wang; Li-Jia Gu; Shao-Hong Huang; Xiu-Ling Chen; Yun Li; Song-Wang Cai; HIF-1? siRNA and cisplatin in combination suppress tumor growth in a nude mice model of esophageal squamous cell carcinoma.. *Asian Pacific Journal of Cancer Prevention* **2012**, *13*, 473-477, 10.7314/apjcp.2012.13.2.473.
53. Carina Fischer; Katharina Leithner; C. (Christoph) Wohlkoenig; Franz Quehenberger; Alexandra Bertsch; Andrea Olschewski; Horst Olschewski; Andelko Hrzenjak; Panobinostat reduces hypoxia-induced cisplatin resistance of non-small cell lung carcinoma cells via HIF-1α destabilization. *Molecular Cancer* **2014**, *14*, 4, 10.1186/1476-4598-14-4.
54. Junlian Gu; Yang Li; Jun Zeng; Bo Wang; Kun Ji; Yufeng Tang; Qing Sun; Knockdown of HIF-1α by siRNA-expressing plasmid delivered by attenuated Salmonella enhances the antitumor effects of cisplatin on prostate cancer. *Scientific Reports* **2017**, *7*, 1-13, 10.1038/s41598-017-07973-4.
55. Yunyao Liu; Xiaoping Wang; Wenshu Li; Yujiao Xu; Yating Zhuo; Mengyuan Li; Yuan He; Xiaosheng Wang; Qinglong Guo; Li Zhao; et al. Oroxylin A reverses hypoxia-induced cisplatin resistance through inhibiting HIF-1α mediated XPC transcription. *Oncogene* **2020**, *39*, 6893-6905, 10.1038/s41388-020-01474-x.
56. Wenjing Su; Lei Huang; Qilin Ao; Qinghua Zhang; Xun Tian; Yong Fang; Yunping Lu; Noscapine sensitizes chemoresistant ovarian cancer cells to cisplatin through inhibition of HIF-1α. *Cancer Letters* **2011**, *305*, 94-99, 10.1016/j.canlet.2011.02.031.
57. Yan Huang; Ying Tian; Yuanyuan Zhao; Cong Xue; Jianhua Zhan; Lin Liu; Xiaobo He; Li Zhang; Efficacy of the hypoxia-activated prodrug evofosfamide (TH-302) in nasopharyngeal carcinoma in vitro and in vivo. *Cancer Communications* **2018**, *38*, 15, 10.1186/s40880-018-0285-0.
58. Massimiliano Mazzone; Daniela Dettori; Rodrigo Leite De Oliveira; Sonja Loges; Thomas Schmidt; Bart Jonckx; Ya-Min Tian; Anthony A. Lanahan; Patrick Pollard; Carmen Ruiz De Almodovar; et al. Heterozygous Deficiency of PHD2 Restores Tumor Oxygenation and Inhibits Metastasis via Endothelial Normalization. *Cell* **2009**, *136*, 839-851, 10.1016/j.cell.2009.01.020.
59. Massimiliano Mazzone; Daniela Dettori; Rodrigo Leite De Oliveira; Sonja Loges; Thomas Schmidt; Bart Jonckx; Ya-Min Tian; Anthony A. Lanahan; Patrick Pollard; Carmen Ruiz De Almodovar; et al. Heterozygous Deficiency of PHD2 Restores Tumor Oxygenation and Inhibits Metastasis via Endothelial Normalization. *Cell* **2009**, *136*, 839-851, 10.1016/j.cell.2009.01.020.