Critical Reviews in Oncology/Hematology 113 (2017) 22–27

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Role of hypoxia-inducible factors (HIF) in the maintenance of stemness and malignancy of colorectal cancer

Ramakrishna Vadde[a,1], Sarojamma Vemula[b,1], Rajeswari Jinka[c,1], Neha Merchant[d], Pallaval Veera Bramhachari[e,1], Ganji Purnachandra Nagaraju[d,*]

[a] Department of Biotechnology and Bioinformatics, Yogi Vemana University, Kadapa, Andhra Pradesh 516003, India
[b] Department of Microbiology, Sri Venkateswara Medical College, Tirupathi, Andhra Pradesh 517507, India
[c] Department of Biochemistry, Acharya Nagarjuna University, Guntur, Andhra Pradesh 522024, India
[d] Department of Hematology and Medical Oncology, Winship Cancer Institute, Emory University, Atlanta, GA 30322, USA
[e] Department of Biotechnology, Krishna University, Machilipatnam, Andhra Pradesh 521 001, India

Contents

ARTICLE INFO

Article history:
Received 11 January 2017

Keywords:
Hypoxia
Hypoxia inducible factors
Cancer stem cells
Colon cancer

ABSTRACT

Hypoxia is a condition of insufficient tissue oxygenation, which is observed during normal development as well as tumorigenesis and its response at the cellular level is primarily mediated through hypoxia inducible factors (HIFs). HIFs have a significant role in the maintenance of stemness in both stem cells as well as in cancer stem cells (CSC) by acting as transcription factors. The CSCs are proposed to be the driving force of colon tumorigenesis and malignancy. These HIFs play a significant role in a wide range of diseases including colon cancer. HIF's signaling functions with stemness, and maintaining Wnt/β-catenin signaling pathways. Due to HIFs functional significance in stemness maintenance in malignancy, targeting HIFs might provide a new approach for development of new therapy for colon cancer. In this review, we will be briefing on the colon and its stem cells, various molecular signaling pathways involved in stemness preservation, and the role hypoxia and its HIFs in the maintenance of stemness in colon stem cells and colon cancer stem cells.

© 2017 Elsevier B.V. All rights reserved.

1. Introduction

Colon cancer is the most commonly diagnosed cancer in both men and women, which causes serious concerns demographically and economically throughout the world. It is the third leading cause of cancer deaths in the US. Colon cancer is a malignance that arises in the colon and rectum. In 2016, an estimated 70,820 men and 63,670 women were diagnosed with colorectal cancer, while 26,020 men and 23,170 women died due to this disease (Siegel et al., 2016). The colon cancer is characterized by inactivation of tumor suppressor genes and activation of oncogenic genes through mutations, resulting in the formation of adenomatous polyps, which are formed in the innermost layer of colon (mucosa), later these polyps eventually develop into adenoma with high-grade dysplasia and further grow into an invasive cancer (Markowitz and Bertagnolli, 2009). Colorectal cancer is associated with various life-style related risk factors includes age, diet, genetic predisposition, smoking,

* Corresponding author.
E-mail address: pganji@emory.edu (G.P. Nagaraju).
[1] Authors contributed equally.

http://dx.doi.org/10.1016/j.critrevonc.2017.02.025
1040-8428/© 2017 Elsevier B.V. All rights reserved.

alcohol consumption, etc. Recent developments in colorectal cancer research promises that there is a significant improvement in the results of empirical therapeutics through new targeted therapies. Targeting cell signaling pathways involved in colorectal cancer assures confidence for evolving remedies with increased specificity and reduced toxicity.

1.1. Stem cells, stem cell niche, and colon cancer stem cells

Stem cells are homogenous cells that yield progeny through two vital features, self-renewal and differentiation (Moore and Lemischka, 2006). Stem cells exist in both embryonic tissues, termed embryonic stem cells (ESC), and in adult tissues, called tissue specific or adult stem cells (Chambers and Smith, 2004). The stem cells present in colon are called colon specific stem cells or colon stem cells (Barker et al., 2008). These colon adult stem cells multiply into new stem cells by replacing the dying cells, and by regenerating damaged tissues. The properties of ESCs and adult stem cells (colon stem cells) are maintained through their local microenvironment, called stem cell niche (Voog and Jones, 2010). The niche is a specialized region where stem cell maintenance is observed. It is composed of cellular and non-cellular components with epithelial cells and duodenal sub-epithelial myofibroblasts (Voog and Jones, 2010). These niche components interact with stem cells and provide suitable environmental signals to regulate and preserve the stemness of stem cells. This niche guards the stem cells from exhaustion and also creates a dynamic system required for sustaining tissue integrity (Oh et al., 2014). Dysregulation of differentiation and self-renewal properties of stem cells lead to colon carcinogenesis (Todaro et al., 2010). Once these cells transform through mutations, these mutated stem cells divide to produce cancer stem cells (CSC) (Todaro et al., 2010). CSCs exactly mimic the functions of normal adult stem cells with their undifferentiating property. These mutated stem cells also have the ability to self-renew and regenerate tumor mass (Todaro et al., 2010). CSCs have been proposed as the driving force of tumorigenesis and the seeds of metastases. Accumulated experimental evidence in recent years have suggested that various cancers, including colon cancer, are regulated by these self-renewing cancer cells (CSC) (Ajani et al., 2015). CSCs are involved in tumor resistance and cancer relapse. Hence, there is a need to develop new therapeutic strategies to successfully target these CSCs responsible for tumor progression

1.2. Stemness maintenance by various pathways

The stem cell proliferation and stemness properties are harmonized by highly conserved signaling pathways like, Wnt signaling, Notch signaling and TGFβ pathway these pathways are known to govern stemness (Crosnier et al., 2006). Wnt signaling pathway proteins are a group of intracellular signaling proteins establishing key role involved in the crypt biology and also perform a central role in stemness preservation and stem cell reservoir maintenance (Holland et al., 2013). Previously noted intestinal sub epithelial myofibrobasts help in maintaining the stem cell niche due to its ability of secreting Wnt ligands. Wnt signaling begins on Wnt ligands that interact with their Frizzled receptor complex. Downstream effector of Wnt pathway is the β-catenin. The stability in cytosol is dependent on the formation of destruction complex between proteins of APC, casein kinase 1 (CK1), glycogen synthase kinase 3 (GSK3) and axin. In absence of Wnt ligand, the active form of GSK3 in destruction complex, phosphorylates cytoplasmic β-catenin, and drives the destruction process further through ubiquitination. In the presence of Wnt ligand there is an inhibition in the form of destruction complex due to inactivation of GSK3 and elevated levels of β-catenin cytosol. These β-catenin molecules translocate from cytoplasm to nucleus, binds to transcription factors of T cell factor family (TCF4) and then transcribe Wnt target genes, such as cMyc, cyclinD1 and survivin (Fig. 1), which main-

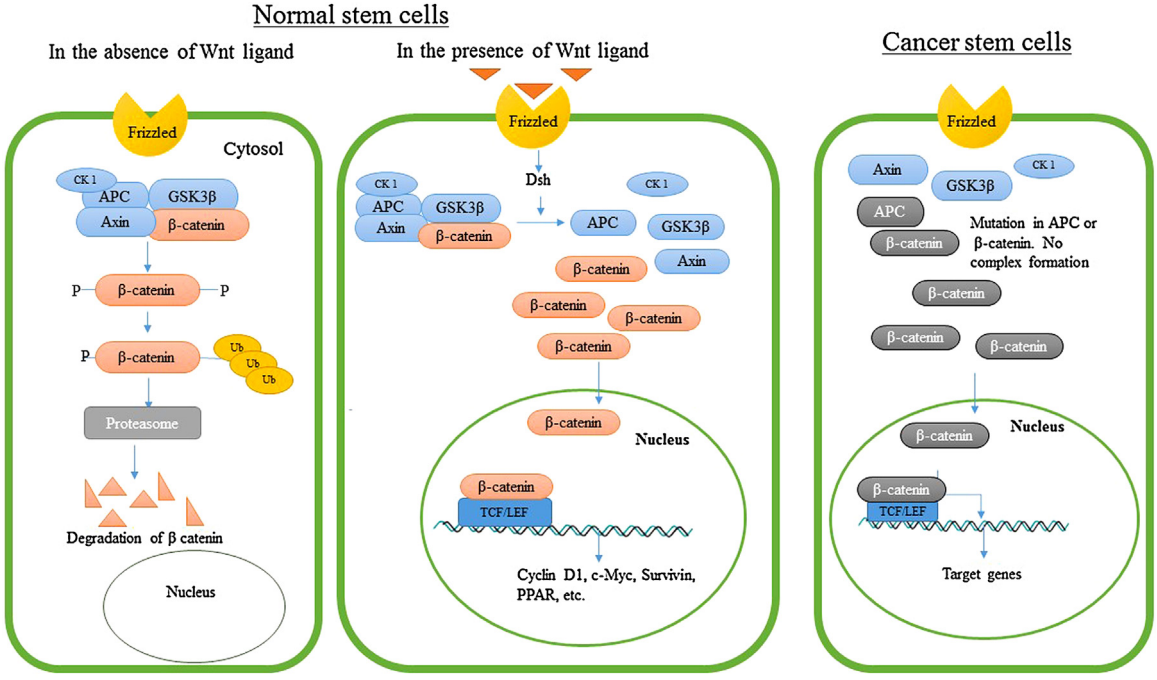

Fig. 1. Mechanism of Wnt/β-catenin signalingpathway in colon cancer. In normal stem cells, the Wnt/β-catenin signaling pathway starts with the binding of a Wnt ligand to a Frizzled-related protein. After binding of Wnt ligand to receptor, Disheveled (Dsh) gets activated by phosphorylation, this in turn inactivates GSK-3β, a key modulator of this signaling pathway. As a result, β-catenin levels increases intracellularly and allowing translocate into the nucleus. There it interacts with T-cell factor/lymphoid enhancer-binding factor (TCF/LEF) and activates the transcription of *Wnt* target genes which are necessary for cellular proliferation and survival (cyclin D1, cMyc, etc.). However, in the absence of a Wnt ligand, GSK-3β forms destruction complex with proteins of axin, adenomatous polyposis coli (APC) and β-catenin. GSK-3β activity is switched on and phosphorylates β-catenin, which in turn ubiquitinated and degraded via the proteasome. In the case of colon cancer, aberrant Wnt/β-catenin signaling contributes to the hyper-proliferative and hypo-apoptotic phenotype, as a result in part of constitutive β-catenin or mutated APC may induce transactivation of pro-survival genes.

tain the stemness and malignancy (Tarapore et al., 2011; Kasdagly et al., 2014; Vanamala, 2015). In case of cancer stem cells (CSC), mutations in either APC or in β-catenin does not form destruction complex. This leads to elevation of β-catenin levels in cytoplasm, later these β-catenin translocate to nucleus and activate the target genes involved in stemness maintenance and differentiation.

Notch signaling is another important highly conserved signaling pathway; it is involved in stem cell regulation. Notch signaling activation stimulates proliferation and inhibits differentiation. Recent study reveals that knockdown of Notch signaling aids in diminishing proliferation and clonogenicity, and increases apoptosis. however, overexpression of Notch show opposite effect (Zhang et al., 2010). They also observed reduced proliferation, CSC self-renewal inhibition and increased differentiation to goblet cells in Notch signaling inhibits APC multiple intestinal neoplasia (APC) in mice. Notch signaling is prominently involved in the regulation of CSC cells (van Es et al., 2005). The TGF-β signaling pathway is another key pathway that is involved in the maintenance of colon stem cell function and carcinogenesis (Calon et al., 2012). This is because of its involvement in cell proliferation, differentiation, migration and apoptosis (Boman and Huang, 2008). Recently, Mishra et al. (2005) observed that the TGF-β signaling pathway is actively involved in gut endoderm development and differentiation of stem cells to differentiate phenotype. They also suggested that colon tumorigenesis is promoted in colonic stem cells synergistically with both TGF-β and Wnt signaling pathways (Mishra et al., 2005). Along with these signaling pathways, Oct4, Sox2 and Nanog also helped in the regulation of stemness.

The stem cell theory of cancer states that aberrant stem cell populations are the cause of colorectal cancers, as stem cells are more susceptible to acquire mutations and manifest the disease, this is because of their long life span as well as self-renewal property. Aberrant Wnt/β-catenin signaling describes colon cancer stem cells (CCSC) in the tumor situation (Valkenburg et al., 2011). These CCSCs are resistant to drug and radiotherapy and are also responsible for relapse of disease. Therefore, it was difficult to eradicate the disease (Li et al., 2009). Since it is imperative, the secondary prevention strategies target aberrant β-catenin signaling, p53 inactivation, and cancer stem cell populations. Recent studies also reveal that hypoxia is involved in progressive tumor growth and regulates stemness (Nagaraju et al., 2015). For better understanding the role of hypoxia in the stemness maintenance in colon cancer, this review briefly describes the role of hypoxia and its hypoxia inducible factors (HIF) in the maintenance of stemness in stem cells and cancer stem cells, which is responsible for malignancy of colon cancer.

1.3. Hypoxia and cancer

Oxygen homeostasis maintenance is critical for organism survival essentially for physiological and pathological backgrounds (Semenza, 2010). Accumulated evidence shows up to 50–60% of solid tumors consisting of hypoxic tissue areas (Vaupel et al., 2004). Hypoxia is a condition in which tissues are not oxygenated adequately due to insufficient concentrations of oxygen in blood. Hypoxia plays a major role in cancer by initiating changes in the microenvironment, altering the oncogenic genes and metabolism, in the form of non-functional blood vessels and there by inducing metastasis (Harris, 2002). In normal tissues, supply of O2 is required for metabolism, however, in tumors, the rate of O2 consumption in neoplastic cells increases a limited O2 supply and results in the development of hypoxia in that tissue area (Vaupel et al., 2004). This feature in tumor is as an important factor since it stimulates cancer promotion and drug resistance. In tumor biology, hypoxia can be represented as a "Janus face" because hypoxia is (a) connected in proliferation, differentiation, apoptosis, and (b) also important in the development of an aggressive tumor phenotype (Vaupel and Mayer, 2007). Due to major role of hypoxia in drug resistance, angiogenesis, invasiveness, metastasis, cell death resistance, metabolism alteration and genome instability, hypoxia may be considered as the best validated target (Wilson and Hay, 2011). All these effects of hypoxia are controlled by hypoxia inducible factor (HIF) proteins. HIFs play a vital role in affecting the regulation of relevant target genes and key transcription factors involved in stem cell self-renewal and differentiation processes.

1.4. Hypoxia-inducible factors (HIF)

Organisms encounter low O_2 tensions is called hypoxia. Hypoxia response at cellular level is mediated through hypoxia-inducible factor (HIF) (Semenza, 2012). HIFs are involved in the regulation of multiple steps involved in tumorigenesis, including neovascularization, invasion, resistance to drugs, etc (Nagaraju et al., 2015). HIFs are also associated in the changes of cell metabolism (Gordan et al., 2007). HIFs consists of two heterodimeric transcription factors, they are (1) α subunit (HIF-1α, HIF-2α, or HIF-3α), which is O_2 labile and (2) β subunit (HIF-1β), which is constitutively expressed and is also known as aryl hydrocarbon receptor nuclear translocator (ARNT) (Rankin and Giaccia, 2008). In HIF-α family, the HIF-1α factors are the best studied factors. Under normal O2 levels (normoxia), the prolyl hydroxylase domain-containing enzymes (PHDs) hydroxylates the key proline residues in HIFα subunit. Later these hydroxylated HIFs are recognized by E3 ubiquitin ligase complex containing the von Hippel–Lindau protein (pVHL) and promote its 26S proteasomal degradation through ubiquitination. However, in hypoxic conditions, HIF-α stabilization is observed because of the absence or low levels of O2 and the PHDs don't show HIFα hydroxylation and cofactors (Appelhoff et al., 2004). After stabilization of HIF-α, it further hetero dimerizes with HIF-β (ARNT) (Wood et al., 1996). This dimer in nucleus binds to DNA at HRE element (hypoxia responsive elements) along with CBP/p300 and activates stem cell maintenance genes, and also genes involved in metabolic reprogramming, genetic instability and tumorigenesis (Fig. 2). In response to hypoxia, both HIF-1α and HIF-2α act redundantly at cellular level because of the structural similarities. Both HIF-1α and HIF-2α induces expression of different sets of genes. HIF-1α regulates the glycolytic enzyme (Hu et al., 2003) and HIF-2α activates Oct4 gene, which is the stem cell factor important for stemness maintenance (Covello et al., 2006). Hypoxia plays a role in stemness maintenance as well as effects the stem cell differentiation. Adult stem cells or tissue specific stem cells are located in the innermost side of the tissue. Most of these potent stem cells are in quiescent and maintain dormancy. The hypoxia (variable O_2 levels) in microenvironment niche might be responsible in regulating stem cell proliferation and differentiation. Further, we will focus on the recent developments in the hypoxia and its HIF pathway, the key regulator of stemness maintenance in stem cells and cancer stem cells and also malignancy in colon cancer.

1.5. HIF role in maintenance of stemness in stem cells

Hypoxia is associated with stemness and HIFα factors. These two are the key regulators of stem cell differentiation (Yun and Lin, 2014). Isoforms of HIF-1α and HIF-2α play a crucial role in the stemness maintenance (Santoyo-Ramos et al., 2014). HIFα specifically regulates all the relevant genes and transcription factors involved in self-renewal and differentiation processes of stem cells (Santoyo-Ramos et al., 2014). HIF-1α maintains stem cells in an undifferentiated state by interaction with Notch1 signaling proteins. However, HIF-2α binds to Oct4 promoter, marker of the undifferentiated state and inducing expression (Rankin et al., 2008). Another transcription factor Sox2 exercises its control on stemness by modulating Oct4 levels in embryonic stem cells (Masui et al.,

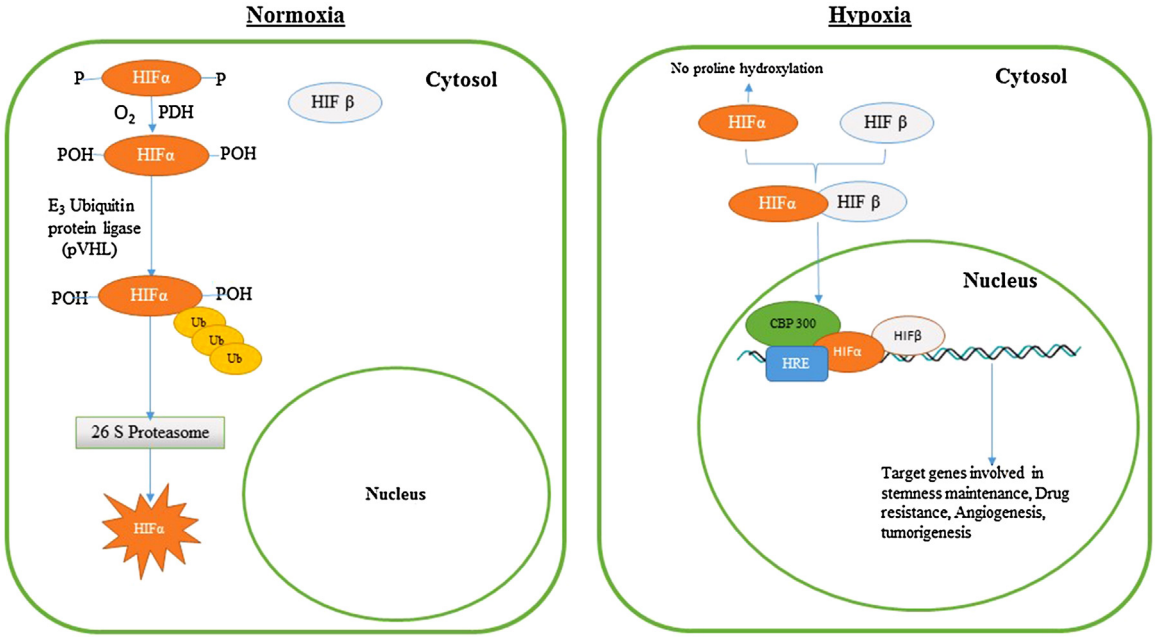

Fig. 2. HIF factors regulation under normal O2 and hypoxic conditions. In the presence of normal O2 levels (normoxia), hydroxylation takes place at conserved proline residues in HIF-α through PHDs, this lead to destabilization of HIFα, and recognized by E3 ubiquitin ligase complex and targets HIFα to go for proteasomal degradation. However, in hypoxia conditions HIF-α stabilization observed by inhibition prolyl hydroxylation (PHD) and proteasomal degradation, this makes HIFα accumulation in cytoplasm and heterodimerization with HIF-1β and then translocated into the nucleus, where it acts as transcription factor binding to the hypoxia responsive DNA element, and recruiting p300/CBP for the activation of a plethora of target genes (hypoxia responsive genes) through transcription.

2007). Takahashi and Yamanaka (2006) experimentally revealed that pluripotent stem cells are formed from somatic cells by cellular reprogramming with transduction of key factors – Oct4, Sox2, c-Myc, and Klf4. Although further studies are required for apprehensive key factors that regulate the differentiation process. Inactivation of the signaling that maintains stemness in hypoxic tissues might help in promoting cell differentiation and could serve as a therapeutic strategy in the prevention of cancer. Recent study suggested that both Sox2 and Klf4 acts as HIF targets (Simon and Keith, 2008). Further, to discover whether Sox2 expression is controlled by HIFα proteins, *in silico* studies were performed for putative HRE binding sequences within Sox2 promoter regions of rat and human and positive results were observed. Further, ChIP and siRNA experiments on knockdown cells of HIF-2α strongly suggest that Sox2 acts a direct target of the HIF-2α. The role of HIF-2α on Sox2 control was further reinforced by the ChIP experiments, which were carried out in the presence of FM19G11, a specific HIFα inhibitor (Moreno-Manzano et al., 2010). All the above statements clearly strengthen the hierarchy of HIF-α in the control of stemness property.

Functional activities of HIF-1α and HIF-2α are abandoned on genetic removal of HIFβ/ARNT and leads to defects in embryonic hematopoiesis (Ramírez-Bergeron et al., 2006). Recent studies have indicated that hypoxia regulates HSC function *in vivo* via HIF-1α. This HIF-1α factor is expressed in higher levels in HSCs (Takubo et al., 2010). However, HIF-1α deletion in stem cell lead to decreased HSCs and ultimate depletion of HSCs. From these experiments Suda and co-workers (Suda et al., 2011) revealed that the hypoxic microenvironment niche of the bone marrow assist HIF-1α stabilization in HSCs, and this stabilization play a key role in HSC maintenance and stress resistance. In hypoxia, HIF-1α mediates a switch from oxidative phosphorylation to glycolytic metabolism and allows redox homeostasis maintenance and makes cell survival under hypoxic environments (Suda et al., 2011). It is also reported that HIF-1α reprograms cell metabolism by activating the genes of glycolytic enzymes and glucose transporters (Seagroves et al., 2001). Under hypoxia conditions, HSC cell expresses elevated levels

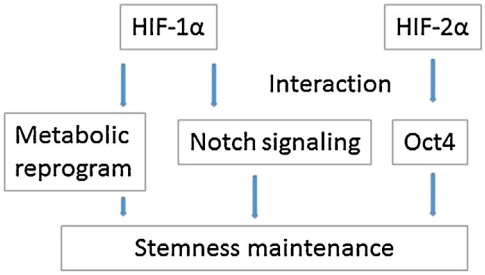

Fig. 3. HIF role in stemness maintenance in stem cells. Under hypoxia conditions, HIF-1α interacts with Notch signaling and influence on the maintenance of stemness by allowing expression of relevant genes and transcription factors involved in stemness maintenance and differentiation. HIF-1α also makes cell survival (stemness) under hypoxic conditions by reprogramming metabolism of glucose. However, the HIF-2α directly involved activation of Oct4 and further responsible for stemness maintenance in stem cells.

of HIF-1α and is responsible for utilization of glucose through glycolysis instead of mitochondrial oxidative phosphorylation, which was evident in HSC demonstrating low mitochondrial potential. Fig. 3 illustrates the role of HIFs in the maintenance of stemness in the stem cells.

1.6. HIF role in stemness and malignancy of cancer stem cells

Cancer stem cells (CSC) are quiescent in stage, but these cells are principally involved in initiation and maintenance of tumor, and also responsible for tumor recurrence and drug resistance (Lobo et al., 2007). Conventional therapies directly attack the proliferating tumor cells and not quiescent CSCs, eventually these cells are responsible for disease recurrence. Therefore, it is required to understand that the mechanisms that support CSCs are important in cancer therapeutic advancement. Simon and Keith (2008) observed in human cancers that self-renewal and differentiation have been regulated by hypoxia and its signaling pathway (Simon and Keith, 2008). In line, Li et al. (2009) demonstrated that the

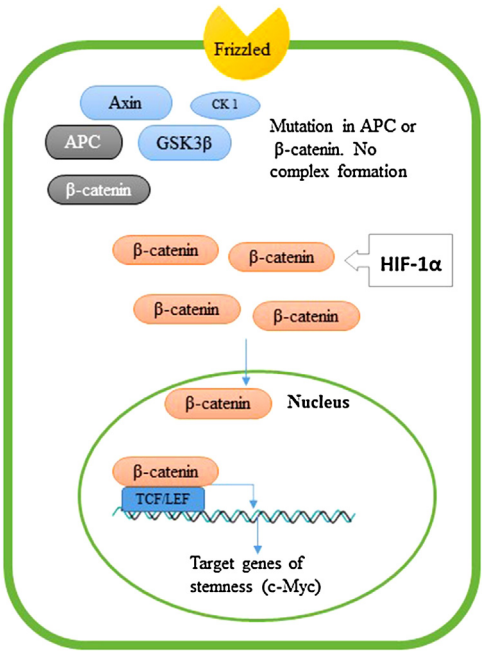

Fig. 4. HIFs in stemness maintenance through Wnt/β-catenin signaling. HIF activates the elevation of β-catenin levels in cytoplasm and translocated in a nucleus. In nucleus, β-catenin binds to TCF/LEF and promotes transcription of all the target genes (c-Myc) involved in stem cell maintenance.

inhibition of CD133+ glioma stem cells (GSCs) self-renewal and potential of tumor initiation in HIF-2α preferential expression and ablation of HIF-2α. In continuation, Samanta et al. (2014) reported that HIF-1α and HIF-2α contribute to the development of CSCs through IL-8 and IL-6 expressions, these are responsible for maintaining stemness and tumor initiation potential in breast cancer cells. HIF-2α mediates the tumor initiation potential in CSCs, which express CD133+ (Li et al., 2009). In the studies performed by Seidel et al. (2010) reduced expression of hypoxia induced CD133+ markers in glioma cells on knock down of HIF-1α and/or HIF-2α was observed. However, in colorectal cancer stem cells, HIF-1α helps in the expression of stem cell surface markers (Santoyo-Ramos et al., 2014). Further, it is also identified that on depletion of HIF-1α protein, the expression of CD44 and Oct4 stem cell markers is decreased in colorectal cancer cells (CRC). Singh et al. (2004) revealed in his experiments that the tumor initiating cells are the CSCs, which are isolated from various human cancers including leukemia, breast, and brain (Singh et al., 2004). He also observed differentiation promotion in embryonic stem cells in the presence of leukemia inhibitory factor (LIF), a member of interleukin-6 super family. In solid tumors, LIF play a central role in tumor progression (Singh et al., 2004). Wu et al. (2015) noticed that HIF-2α mediates LIF expression in hypoxic CRC cells. Therefore, both the isoforms of HIF-1α and HIF-2α have a major role in tumor relapse by SC marker expression in colorectal cancer. It is also observed that HIF-2α promotes drug resistance and radio-resistance in tumor cells with the suppression of p53 tumor suppressor gene (Bertout et al., 2009). Besides this, HIF-2α is also activates Oct4 genes (Covello et al., 2006). The role of Oct4, Sox2, c-Myc in generating iPSC from differentiated cells has been identified by Takahashi and Yamanaka (2006) and the same genes are also activated by HIF-2α in renal carcinoma cells. Saito et al. (2015) reviewed in their article that hypoxia and its HIF factors not only regulate stem cell proliferation and differentiation but also analyzed its beneficial role in stemness property acquisition and reprogramming of cells.

It has been observed in recent reports that hypoxia play a vital role in the regulation of activities of transcription factors involved in stem cell maintenance (Covello et al., 2006). It has also been observed that hypoxia induced factors particularly HIF-1α is involved in Wnt activation and promotes self-renewal maintenance (Mazumdar et al., 2010). Mazumdar and his coworkers (Mazumdar et al., 2010) observed that Wnt singaling is actively modulated through HIF-1α by elevated levels in cytoplasm and translocated into the nucleus. In nucleus, β-catenin binds to LEF-1 and TCF-1 and activates expression of effector target genes in embryonic stem cells (Fig. 4). Epithelial to mesenchymal transition program in microenvironment niche gets stimulated in the presence of both HIF and Wnt signaling factors (Zhang et al., 2013). During tumor growth and metastasis, a cross-talk was noticed between HIF signaling and canonical Wnt signaling and expresses the target genes through synergistic interaction (Dang et al., 2008). However, Santoyo-Ramos et al. (2014) show that stemness and malignancy in colon cancer are modulated through HIFs by playing an o pposite role in Wnt/β-catenin signaling.

2. Summary and future perspectives

Hypoxia plays an important role in development, physiology and disease and its chief mediators are HIF. By engrossing previous excellent studies obtained from various experiments, we observed that HIFs plays a significant role in a wide range of diseases including colorectal cancer. It is particularly involved in the stemness maintenance and malignancy in colon cancer. HIF signaling functioning with stemness helps in maintaining Wnt signaling pathways. Both HIFs show opposite effects on cancer growth and progression. Treatment strategies should be focused on inhibiting HIFs and applied to clinical therapy. Finally, future studies will define the HIF pathway regulation in modulation of stem cell function in normal cell development and in tumorigenesis to develop effective therapeutic strategies for cancer treatment.

Conflict of interest statement

The authors confirm that there are no conflicts of interest.

References

Ajani, J.A., Song, S., Hochster, H.S., Steinberg, I.B., 2015. Cancer stem cells: the promise and the potential. Semin. Oncol.: Elsevier, S3–S17.
Appelhoff, R.J., Tian, Y.-M., Raval, R.R., Turley, H., Harris, A.L., Pugh, C.W., et al., 2004. Differential function of the prolyl hydroxylases PHD1, PHD2, and PHD3 in the regulation of hypoxia-inducible factor. J. Biol. Chem. 279, 38458–38465.
Barker, N., van de Wetering, M., Clevers, H., 2008. The intestinal stem cell. Genes. Dev. 22, 1856–1864.
Bertout, J.A., Majmundar, A.J., Gordan, J.D., Lam, J.C., Ditsworth, D., Keith, B., et al., 2009. HIF2α inhibition promotes p53 pathway activity, tumor cell death, and radiation responses. Proc. Natl. Acad. Sci. U. S. A. 106, 14391–14396.
Boman, B.M., Huang, E., 2008. Human colon cancer stem cells: a new paradigm in gastrointestinal oncology. J. Clin. Oncol. 26, 2828–2838.
Calon, A., Espinet, E., Palomo-Ponce, S., Tauriello, D.V., Iglesias, M., Céspedes, M.V., et al., 2012. Dependency of colorectal cancer on a TGF-β-driven program in stromal cells for metastasis initiation. Cancer Cell 22, 571–584.
Chambers, I., Smith, A., 2004. Self-renewal of teratocarcinoma and embryonic stem cells. Oncogene 23, 7150–7160.
Covello, K.L., Kehler, J., Yu, H., Gordan, J.D., Arsham, A.M., Hu, C.-J., et al., 2006. HIF-2α regulates Oct-4: effects of hypoxia on stem cell function, embryonic development, and tumor growth. Genes. Dev. 20, 557–570.
Crosnier, C., Stamataki, D., Lewis, J., 2006. Organizing cell renewal in the intestine: stem cells, signals and combinatorial control. Nat. Rev. Genet. 7, 349–359.
Dang, C.V., Kim, J.-w., Gao, P., Yustein, J., 2008. The interplay between MYC and HIF in cancer. Nat. Rev. Cancer 8, 51–56.
Gordan, J.D., Thompson, C.B., Simon, M.C., 2007. HIF and c-Myc. sibling rivals for control of cancer cell metabolism and proliferation. Cancer Cell 12, 108–113.
Harris, A.L., 2002. Hypoxia—a key regulatory factor in tumour growth. Nat. Rev. Cancer 2, 38–47.
Holland, J.D., Klaus, A., Garratt, A.N., Birchmeier, W., 2013. Wnt signaling in stem and cancer stem cells. Curr. Opin. Cell Biol. 25, 254–264.
Hu, C.-J., Wang, L.-Y., Chodosh, L.A., Keith, B., Simon, M.C., 2003. Differential roles of hypoxia-inducible factor 1α (HIF-1α) and HIF-2α in hypoxic gene regulation. Mol. Cell. Biol. 23, 9361–9374.

Kasdagly, M., Radhakrishnan, S., Reddivari, L., Veeramachaneni, D.R., Vanamala, J., 2014. Colon carcinogenesis: influence of western diet-induced obesity and targeting stem cells using dietary bioactive compounds. Nutrition 30, 1242–1256.
Li, Z., Bao, S., Wu, Q., Wang, H., Eyler, C., Sathornsumetee, S., et al., 2009. Hypoxia-inducible factors regulate tumorigenic capacity of glioma stem cells. Cancer Cell 15, 501–513.
Lobo, N.A., Shimono, Y., Qian, D., Clarke, M.F., 2007. The biology of cancer stem cells. Annu. Rev. Cell Dev. Biol. 23, 675–699.
Markowitz, S.D., Bertagnolli, M.M., 2009. Molecular basis of colorectal cancer. New Engl. J. Med. 361, 2449–2460.
Masui, S., Nakatake, Y., Toyooka, Y., Shimosato, D., Yagi, R., Takahashi, K., et al., 2007. Pluripotency governed by Sox2 via regulation of Oct3/4 expression in mouse embryonic stem cells. Nat. Cell Biol. 9, 625–635.
Mazumdar, J., O'Brien, W.T., Johnson, R.S., LaManna, J.C., Chavez, J.C., Klein, P.S., et al., 2010. O2 regulates stem cells through Wnt/[beta]-catenin signalling. Nat. Cell Biol. 12, 1007–1013.
Mishra, L., Derynck, R., Mishra, B., 2005. Transforming growth factor-ß signaling in stem cells and cancer. Science 310, 68–71.
Moore, K.A., Lemischka, I.R., 2006. Stem cells and their niches. Science 311, 1880–1885.
Moreno-Manzano, V., Rodríguez-Jiménez, F.J., Aceña-Bonilla, J.L., Fustero-Lardíes, S., Erceg, S., Dopazo, J., et al., 2010. FM19G11, a new hypoxia-inducible factor (HIF) modulator, affects stem cell differentiation status. J. Biol. Chem. 285, 1333–1342.
Nagaraju, G.P., Bramhachari, P.V., Raghu, G., El-Rayes, B.F., 2015. Hypoxia inducible factor-1α: its role in colorectal carcinogenesis and metastasis. Cancer Lett. 366, 11–18.
Oh, J., Lee, Y.D., Wagers, A.J., 2014. Stem cell aging: mechanisms, regulators and therapeutic opportunities. Nat. Med. 20, 870–880.
Ramírez-Bergeron, D.L., Runge, A., Adelman, D.M., Gohil, M., Simon, M.C., 2006. HIF-dependent hematopoietic factors regulate the development of the embryonic vasculature. Dev. Cell 11, 81–92.
Rankin, E., Giaccia, A., 2008. The role of hypoxia-inducible factors in tumorigenesis. Cell Death Differ. 15, 678–685.
Rankin, E.B., Rha, J., Unger, T.L., Wu, C.H., Shutt, H.P., Johnson, R.S., et al., 2008. Hypoxia-inducible factor-2 regulates vascular tumorigenesis in mice. Oncogene 27, 5354–5358.
Saito, S., Lin, Y.-C., Tsai, M.-H., Lin, C.-S., Murayama, Y., Sato, R., et al., 2015. Emerging roles of hypoxia-inducible factors and reactive oxygen species in cancer and pluripotent stem cells. Kaohsiung J. Med. Sci. 31, 279–286.
Samanta, D., Gilkes, D.M., Chaturvedi, P., Xiang, L., Semenza, G.L., 2014. Hypoxia-inducible factors are required for chemotherapy resistance of breast cancer stem cells. Proc. Natl. Acad. Sci. U. S. A. 111, E5429–E5438.
Santoyo-Ramos, P., Likhatcheva, M., García-Zepeda, E.A., Castañeda-Patlán, M.C., Robles-Flores, M., 2014. Hypoxia-inducible factors modulate the stemness and malignancy of colon cancer cells by playing opposite roles in canonical Wnt signaling. PLoS One 9, e112580.
Seagroves, T.N., Ryan, H.E., Lu, H., Wouters, B.G., Knapp, M., Thibault, P., et al., 2001. Transcription factor HIF-1 is a necessary mediator of the pasteur effect in mammalian cells. Mol. Cell. Biol. 21, 3436–3444.
Seidel, S., Garvalov, B.K., Wirta, V., von Stechow, L., Schänzer, A., Meletis, K., et al., 2010. A hypoxic niche regulates glioblastoma stem cells through hypoxia inducible factor 2α. Brain 133, 983–995.
Semenza, G.L., 2010. Oxygen homeostasis. Wiley Interdiscip. Rev. Syst. Biol. Med. 2, 336–361.
Semenza, G.L., 2012. Hypoxia-inducible factors in physiology and medicine. Cell 148, 399–408.
Siegel, R.L., Miller, K.D., Jemal, A., 2016. Cancer statistics, 2016. CA Cancer J. Clin. 66, 7–30.
Simon, M.C., Keith, B., 2008. The role of oxygen availability in embryonic development and stem cell function. Nat. Rev. Mol. Cell Biol. 9, 285–296.
Singh, S.K., Hawkins, C., Clarke, I.D., Squire, J.A., Bayani, J., Hide, T., et al., 2004. Identification of human brain tumour initiating cells. Nature 432, 396–401.
Suda, T., Takubo, K., Semenza, G.L., 2011. Metabolic regulation of hematopoietic stem cells in the hypoxic niche. Cell Stem Cell 9, 298–310.
Takahashi, K., Yamanaka, S., 2006. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell 126, 663–676.
Takubo, K., Goda, N., Yamada, W., Iriuchishima, H., Ikeda, E., Kubota, Y., et al., 2010. Regulation of the HIF-1α level is essential for hematopoietic stem cells. Cell Stem Cell 7, 391–402.
Tarapore, R.S., Siddiqui, I.A., Mukhtar, H., 2011. Modulation of Wnt/β-catenin signaling pathway by bioactive food components. Carcinogenesis, bgr305.
Todaro, M., Francipane, M.G., Medema, J.P., Stassi, G., 2010. Colon cancer stem cells: promise of targeted therapy. Gastroenterology 138, 2151–2162.
Valkenburg, K.C., Graveel, C.R., Zylstra-Diegel, C.R., Zhong, Z., Williams, B.O., 2011. Wnt/β-catenin signaling in normal and cancer stem cells. Cancers 3, 2050–2079.
van Es, J.H., van Gijn, M.E., Riccio, O., van den Born, M., Vooijs, M., Begthel, H., et al., 2005. Notch/γ-secretase inhibition turns proliferative cells in intestinal crypts and adenomas into goblet cells. Nature 435, 959–963.
Vanamala, J., 2015. Food systems approach to cancer prevention. Crit. Rev. Food Sci. Nutr.
Vaupel, P., Mayer, A., 2007. Hypoxia in cancer: significance and impact on clinical outcome. Cancer Metastasis Rev. 26, 225–239.
Vaupel, P., Mayer, A., Höckel, M., 2004. Tumor hypoxia and malignant progression. Methods Enzymol. 381, 335–354.
Voog, J., Jones, D.L., 2010. Stem cells and the niche: a dynamic duo. Cell Stem Cell 6, 103–115.
Wilson, W.R., Hay, M.P., 2011. Targeting hypoxia in cancer therapy. Nat. Rev. Cancer 11, 393–410.
Wood, S.M., Gleadle, J.M., Pugh, C.W., Hankinson, O., Ratcliffe, P.J., 1996. The role of the aryl hydrocarbon receptor nuclear translocator (ARNT) in hypoxic induction of gene expression studies in ARNT-deficient cells. J. Biol. Chem. 271, 15117–15123.
Wu, L., Yu, H., Zhao, Y., Zhang, C., Wang, J., Yue, X., et al., 2015. HIF-2alpha mediates hypoxia-induced LIF expression in human colorectal cancer cells. Oncotarget 6, 4406–4417.
Yun, Z., Lin, Q., 2014. Hypoxia and regulation of cancer cell stemness. Tumor Microenv. Cell. Stress: Springer, 41–53.
Zhang, Y., Li, B., Ji, Z.Z., Zheng, P.S., 2010. Notch1 regulates the growth of human colon cancers. Cancer 116, 5207–5218.
Zhang, Q., Bai, X., Chen, W., Ma, T., Hu, Q., Liang, C., et al., 2013. Wnt/β-catenin signaling enhances hypoxia-induced epithelial-mesenchymal transition in hepatocellular carcinoma via crosstalk with hif-1α signaling. Carcinogenesis 34, 962–973.