TRANSCRIPTION FACTOR ZBTB20: WHAT EXPRESSION IS TELLING US OF ITS CELLULAR FUNCTION?

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Transcription factors are key regulators of cell fate maintenance and transition. Thus, they represent key molecular targets in the fields of stem cell biology and regenerative medicine. The constant need to generate protocols with higher stem cell yield, faster and more efficient differentiation led to in-depth understanding of the function of many transcription factors in regulating developmental and adult stem cells. In this Dance Round we summarize the current understanding of the expression of a zinc finger and BTB domain-containing transcription factor ZBTB20, and comment on how its expression provides clues for its involvement in stem cell biology. Biomed Rev 2020; 31: 1-10

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INTRODUCTION

During normal development, stem/progenitor cells undergo multiple divisions and gradual fate restrictions eventually differentiating and leading to the generation of adult tissues. While development progresses progenitors switch between several modes of division to ensure proper balance between the dividing cell pool and the differentiated cell output (1–5). In adults, stem cells reside in specific tissue microdomains named “stem cell niches”. A fraction of adult stem cells are quiescent and these are triggered to proliferate upon activation such as injury (6–8). Exit from quiescence is accompanied by a switch of the genetic programs in quiescent versus activated stem cells (9–12). Among the well-established mechanisms to achieve this change in gene expression is delivered by a family of DNA binding proteins named transcription factors (TFs) (13–15). More than 3000 TFs are known to date and their classification is not in the scope of this Dance Round. TFs share similar structural features: (i) one or several DNA binding domains; (ii) domain(s) for protein-protein interactions. Here we discuss one particular TF, named ZBTB20,
also known as HOF (16). ZBTB20 has its name because it contains both a BTB (Broad-Complex, Tramtrack and Bric a brac) domain in its N-terminal region which is responsible for homo- and heteromeric protein-protein interactions, and the C-terminal region is occupied by five C2H2 Zinc finger motifs making up the DNA binding domain of this protein (16–18). Zbtb20 was identified in dendritic cells and named DPZF (dendritic cell-derived BTB/Poz zinc finger protein) (19). Two transcripts are generated due to alternative splicing, named HOFL (long), and HOFS (short) lacking 73 amino acids from the N-termus (16). The two isoforms are considered to have redundant function.

**ZBTB20 EXPRESSION IN THE FOREBRAIN**

The embryonic forebrain has several subdivisions. The dorsal-most part, known as the dorsal pallium (DP), is the progenitor zone of cortical excitatory neurons and is replaced by the neocortex in adulthood (Fig. 1A2). The medial pallium (Fig. 1A2, MP) will give rise to the hippocampus and includes morphologically distinct subdomains: dentate gyrus (DG) and Ammon’s horn (CA) (20). The pallial Zbtb20 expression is initiated as early as embryonic day (E)11.5 in the ventral forebrain and spreads to the lateral pallium (Fig. 1A2; LP). By E14.5 the Zbtb20 expression extends through the entire pallial ventricular zone (VZ) (Fig. 1A1), where it is preserved until late embryonic stage (E18.5).

In the VZ of the DP expression is concomitant with markers of apical and basal radial glia progenitors (Fig. 1A1), including Pax6, Sox2, Coup-TFI (21,22). At early postnatal stages (P0-P4), the Zbtb20 expression in the VZ is reduced but remains strong in the pyramidal neurons of neocortical layers 2-3 (Fig. 1A3) in which it disappears by P12 (22).

The earliest studies investigating Zbtb20 reported a strong expression in the developing hippocampus throughout development (16). Zbtb20 expression is observed in proliferating progenitors between E12.5-E17.5, and is gradually increased in postmitotic cells starting E14.5 (Fig. 1B1) (21,23). At late embryonic stages Zbtb20 was observed in immature migrating hippocampal CA pyramidal neurons and DG neurons (16). In the hippocampus, Zbtb20 exhibits the strongest expression in the CA1 sector (23). At postnatal and adult stages Zbtb20 expression persists in the upper row of CA1 pyramidal cells (Fig. 1B2, inset) (16,24). In the DG, Zbtb20 shows a mosaic

**Figure 1.** A summary of TF Zbtb20 expression in the nervous system. A Expression in the neocortex. A1 A schematic summary of the Zbtb20 expression at different stages of neocortical development. In the pallial radial glial progenitors of VZ, Zbtb20 expression is robust as early as E14. At early postnatal stages Zbtb20 is localized to layer2/3 glutamatergic neurons, while in the adult neocortex the expression in neurons is down-regulated. A2 Histological visualization of Zbtb20 mRNA in the developing mouse cortex at E12.5. The onset of pallial expression of Zbtb20 is evident in the LP. Strong expression in the subpallium is also seen. A3 Immunofluorescence staining of Zbtb20 in the mouse cortex at stage P8. Note the strong signal in neocortical layers 2/3. B Expression in the hippocampus. B1 A schematic summary of the expression at different stages of hippocampal development. In the hippocampal VZ, Zbtb20 is evident as early as E12.5. At early postnatal stages the expression is strong in the dentate gyrus and the upper row of CA1-CA3 pyramidal neurons. In the adult hippocampus the expression in both dentate gyrus and CA sectors is diminished but still present. B2 Immunofluorescence labeling of Zbtb20 (green) in the mouse hippocampus at P8 (all nuclei are labeled by DAPI in blue). A higher magnification inset of the CA1 sector depicts the strong Zbtb20 signal in the upper row pyramidal neurons (an asterisk outlines the lower pyramidal row). C Expression in SVZ brain stem cell niche. C1 A schematic summary of the expression in brain stem cells at different stages of SVZ development. In the embryo and around birth, Zbtb20 is expressed in ventricular radial glia apical progenitors. At postnatal and adult stages the SVZ niche is reorganized and Zbtb20 is present in putative stem cells ad transit-amplifying progenitors (B and C cells) at a higher level, with diminished expression in neuroblasts (A cells). Ependymal expression is also evident. C2 Immunofluorescence labeling of Zbtb20 (green) in the mouse SVZ at P12. A strong signal is observed in both the ependymal (EL) and subependymal (SEL) layers of the SVZ. D Expression in cortical macroglial cells. D1 A schematic summary of the expression at different stages of glial development. Around birth Zbtb20 is expressed in gliogenic radial glia stem cells. After P21 its expression can be found in parenchymal glial progenitors and astrocytes, but not in oligodendrocytes. D2 Immunofluorescence double-labeling for Zbtb20 (red) and the mature astrocyte marker S100β (green) in the mouse cortex at P12. A magnified view of several double positive cells is present in the insets. VZ - ventricular zone; SVZ - subventricular zone; MZ - marginal zone; MP, DP, LP - medial, dorsal and lateral pallium respectively; CP – cortical plate; CC – corpus callosum; L1-6 – Layer 1-6

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expression pattern with some cells characterized by a strong expression level while others - with a low expression level. Apart from its presence in neurogenic progenitors and neurons, Zbtb20 is also expressed in gliogenic progenitors necessary for astrocytogenesis and oligodendrogligenesis (Fig. 1D1) (21,25,26) as well as in the mature astrocytes of the postnatal and adult cortex (Fig. 1D2). Similarly to mice, in humans ZBTB20 is also expressed in the developing hippocampus. Expression was detected as early as 11 WPC (weeks post conception) in the dentate anlage but remained low in the neuroepithelium. At 13WPC expression has spread to all hippocampal germinai zones and the dentate migratory stream. At 20 WPC granule cells, the dentate migratory stream, and immature projection neurons of the CA sector showed a strong ZBTB20 expression (27).

**EXPRESSION OF ZBTB20 IN OTHER BRAIN REGIONS**

A presence of Zbtb20 outside the forebrain is also detected but less well characterized. In the postnatal olfactory bulb, it is restricted to astrocytes and a subpopulation of glomerular interneurons. In the postnatal diencephalon, Zbtb20 was detected in neurons of the hypothalamic suprachiasmatic nucleus (26,28). The cerebellum also shows positive for Zbtb20 cells. The cerebellar granule cells are produced in a transient proliferative zone named external granular layer. Once generated the immature cells migrate deeper in the cerebellar cortex forming the internal granular layer (29). Immature and migrating granule cell are positive for Zbtb20 and this expression pattern requires further investigation (16). In the peripheral nervous system, Zbtb20 was detected in developing dorsal root ganglia, where its expression persists in postnatally in the nociceptive bipolar cells (21,30). Of note, Zbtb20 is also expressed in the subventricular zone, a stem cell niche in the adult brain (26). The highest expression was observed in putative stem cells transient amplifying cells, and niche astrocytes, with a gradual decline of the levels in the neuroblasts (Fig. 1C) (26).

**ZBTB20 EXPRESSION IN THE MUSCULOSKELETAL SYSTEM**

The musculoskeletal system originates from mesodermal structures called somites (31). The early expression of Zbtb20 (E9.5) in these structures was the first evidence for its possible involvement in the development of this system (21). At post-somite stages, Zbtb20 was not detected in muscle fibers but was expressed in satellite cells serving as stem cells during the postnatal development. The expression of Zbtb20 in these cells is most likely involved in maintaining the quiescent stem cell niche in the muscle. Overexpression led to increased activation of the satellite cells and myoblast maturation (32). In the developing mouse skeleton, Zbtb20 was not found in proliferating chondrocytes, osteoblasts, and perioseal cells. Rather, its expression was confined to the differentiating hypertrophic chondrocytes (32). Postnatally, the Zbtb20 expression spread to the reserve cartilage zone, and a much weaker signal was observed in the proliferating zone while maintaining expression in the differentiating hypertrophic chondrocytes (33).

**ZBTB20 EXPRESSION IN THE LIVER**

The liver expression of Zbtb20 is very low during development (34). Postnatally, it rises abruptly reaching a plateau by P8, when a 12-fold increase of Zbtb20 mRNA was observed as compared to P0. The levels of Zbtb20 persist in adulthood when Zbtb20 is involved in repression of the transcription of the alpha-fetoprotein (Fig. 2A) (34). In line with the aforementioned results Zbtb20 expression is reduced during the initial stages of liver regeneration after hepatectomy in adult mice and gradually reached control levels of expression when liver to body weight ratio approached normal values (34).

**ZBTB20 EXPRESSION IN IMMUNE CELLS**

Zbtb20 was detected in the cells of the humoral immune system. The major players in the humoral response are the B lymphocytes, which are activated upon contact with T_{H}2-helpers (35). Upon activation B-cells differentiate into antibody-secreting plasma cells (PCs), memory B-cells or form germinal centers (GC) where they proliferate. Zbtb20 mRNA is present in all B-cells: developing B-cells, B-1 cells in the peritoneum, GC B-cells, and long-lived bone marrow (BM) PCs as well as splenic PCs. Protein expression increases steadily from immature GC B cell, to immature plasmablasts and to BM differentiated PCs (36). Naïve B-cells and B-cell progenitors show relatively low expression levels. (Fig. 2B) (37). Zbtb20 expression was also shown in a subpopulation of memory T-lymphocytes (38). To our knowledge there is no evidence for Zbtb20 expression in the granulocyte lineage and other T-lymphocytes.

**ZBTB20 EXPRESSION IN OTHER ORGANS**

Zbtb20 is expressed in all hormone-producing cells of the anterior pituitary (Fig. 2C) (39). However, this TF appears to be indispensable only for the development of the lactotrophs (Prolactin-producing cells) (40). Expression in the posterior...
Figure 2. Schematic representation of the Zbtb20 expression outside the nervous system. A In liver Zbtb20 is only weakly expressed in during development with a gradual increase postnatally, eventually reaching a plateau. B In the immune system expression is low in centroblasts, increasing in immature B-cells, reaching its highest levels in the long-lived plasma cells. C Expression in the anterior pituitary is confined to all endocrine cells, but the Prolactin-secreting cells are most critically dependent on the presence of Zbtb20. D Expression in the testis tubules is limited to the Sertoli and Leydig cells. GS – Germinal Center GH – Gonadotropic Hormone LH – Luteinizing Hormone, FSH Follicle Stimulating Hormone, TSH Thyroid-stimulating hormone, PLR - Prolactin.
lobe was also reported (Fig. 2C) (39,40). In the testis, Zbtb20 is localized in mature Sertoli cells as well as in the testosterone-producing Leydig cells (Fig. 2D) (41). Human dental pulp stem cells upregulate both mRNA and protein levels of Zbtb20 when induced to differentiate in vitro (42).

**TF ZBTB20 AS A PROLIFERATION/CELL CYCLE REGULATOR**

Zinc finger-BTB TFs function as cell fate determinants by regulating the cell cycle progression in many systems (18,43). The expression pattern of Zbtb20 (Table 1) suggests its involvement in the cell cycle regulation, and accordingly, several experimental manipulations of its levels were performed to test this. A number of loss-of-function studies revealed a decreased proliferation in the absence of Zbtb20 (Table 2). Liver-specific Zbtb20 deletion in mice led to a slower liver regeneration in the initial stages of recovery after partial hepatectomy (44). This effect was attributed to a slower proliferation of hepatocytes.

**Table 1. Summary of available data on the expression of Zbtb20.**

| Location of expression | Developmental stage and characteristics of expression | Reference |
|------------------------|-----------------------------------------------------|------------|
| Hippocampus            | E12.5-E15.5: Apical and a few basal progenitors in VZ/SVZ  
                       | E16.5: migrating and settled pyramidal CA neurons  
                       | E17.5: migrating and settled DG granule cells  
                       | Adult: Upper row CA1 pyramidal and DG granule neurons; expression gradually decreases. | 13, 39  
| Neocortex              | E11.5/E12.5: cortical hem and ventral pallium  
                       | E14.5: entire VZ of the dorsal pallium  
                       | E16.5: VZ and SVZ of the entire pallium  
                       | E18.5: diminishes but remains present in the VZ  
                       | P0-P4: pyramidal neurons in neocortical layers 2-3  
                       | Postnatal and adult: expressed in glial progenitors, astrocytes and ependymal cells | 18, 19, 20  
| Basal ganglia           | E10.5: Progenitors of VZ and SVZ  
                       | 18 |
| Olfactory Bulb         | P4: astrocytes and at low levels in some glomerular neurons | 20 |
| Spinal Ganglia         | E10.5 – E14.5: developing dorsal root ganglion neurons  
                       | Adult: nociceptive dorsal root ganglia neurons | 18, 23  
| Hypothalamus           | Adult: Expressed in suprachiasmatic nucleus of hypothalamus | 23 |
| Cerebellum             | P5-P10: immature migrating and settled cerebellar granule cells in the EGL/IGL: expression is extinguished as they mature | 13 |
| Pituitary Gland        | E14.5: embryonic pituitary gland, expression increases steadily during development.  
                       | Postnatal: all endocrine anterior pituitary gland cells | 33 |
| Liver                  | Fetal: little or no expression  
                       | Postnatal: gradual increase, maximum mRNA level reached at P56 | 27 |
| Hearth                 | E9.5 | 18 |
| Musculoskeletal system | E10.5: somites  
                       | E14.5: hypertrophic zone chondrocytes  
                       | P4-P90: reserve zone and hypertrophic zone chondrocytes  
                       | E16.5-8 months: during establishment and maintained in adult satellite cells; expression gradually increases | 18  
| Dental pulp stem cells | 7-14 days in vitro: dental pulp stem cell differentiation | 25 |
| Immune system          | Various stages after antigen immunization: B cell population, highly enriched in long-lived plasma cells and memory cells | 32 |
| Testis                 | P7-P70: Sertoli and Leydig cells | 35 |
Table 2. Effects of experimentally altered Zbtb20 expression on cell proliferation. CKI – Cyclin Dependent Kinase Inhibitor; CDK – Cyclin Dependent Kinase

| Target cells/stage (Ref.) | Experimental manipulation | Result from manipulation |
|---------------------------|---------------------------|--------------------------|
| Adult hepatocytes (29)    | Zbtb20 loss-of-function in vivo | Proliferation after hepatectomy, Cyclin D1 and CDK4 |
| Chondrocytes in developing cartilage/Stage P22 (26) | Zbtb20 loss-of-function in vivo | Proliferation, Chondrocyte differentiation |
| Dorsal pallium radial glia/Stage E16.5 (19) | Zbtb20 loss-of-function in vivo | Cell cycle exit, Proliferation |
| B-cell plasma cell line (31) | Zbtb20 gain-of-function in vitro | Proliferation, CKI p15 |
| Non-small cell lung carcinoma (37) | Zbtb20 gain-of-function in vitro | Proliferation |

This proliferation defect was concomitant with reduced levels of the cell cycle progression protein cyclin D1 and its counterpart kinase CDK4 (44). This defect was linked to a reduction of epidermal growth factor receptor (EGFR) expression in hepatocytes, and EGFR is known for its role in hepatocyte cycle progression (44). In contrast, knocking down Zbtb20 in liver cell cultures augmented proliferation (45).

Studies in other systems also reported defects in proliferation and differentiation upon Zbtb20 loss-of-function. A cartilage-specific Zbtb20 inactivation showed no defect in proliferation at early stages (P4), but at later stages (P22) it produced a noticeable proliferation reduction of chondrocytes in the proliferating cartilage zone (33). Further, an enhanced chondrocyte differentiation was detected as early as P4. Because the enhanced differentiation was observed in the absence of increased apoptosis, the authors concluded that it was due to a proliferation defect (33). Whether Zbtb20 alters cell cycle parameters was not directly tested in this setting. Zbtb20 loss-of-function also reduced proliferation of neurogenic cortical progenitors. Zbtb20 knockout mice showed a decreased proliferation and enhanced exit from the mitotic cell cycle at mid-neurogenesis (E15.5-E16.6) resulting in few upper layer cortical pyramidal neurons born in the mutant (22). This effect was potentially mediated by a binding of Zbtb20 to the promoter of TF COUP-TFI (22), a known regulator of cell cycle progression in neocortical stem cells (46).

A few reports focus on the effect on proliferation of Zbtb20 gain-of-function. Estrogen receptor (ER)-inducible overexpression of Zbtb20 in plasma cell cultures lead to a much slower rate of proliferation evident by the smaller cell number in the Zbtb20-ER colonies. The putative cause of this phenotype is the slower progression from G1- to S-phase and an overproduction of the inhibitor CKI p15 (36). In non-small cell lung cancer, Zbtb20 overexpression was shown to increase proliferation (47). Upon Zbtb20 overexpression, both Cyclin D1 and Cyclin E were elevated, while the levels of the CDK inhibitors p21 and p27 were down-regulated (47,48). Knockdown of Zbtb20 had an opposite effect. This was likely mediated by FoxO1, a gene inhibiting cell cycle progression, directly repressed by Zbtb20 (47,48).

CONTEXT DEPENDENT REGULATION OF THE CELL CYCLE BY TF ZBTB20

Data from different systems indicate that Zbtb20 is capable of promoting or impeding the cell cycle progression (Table 2). It is fascinating that the same gene may have opposite effects on cell cycle in a cell-dependent manner. Thus, the tissue context and the molecular partners seem critical for the effects of TF Zbtb20 on the cell cycle (see Box). The Zbtb20 expression in stem cell niches of the adult brain, liver and skeletal muscle places this TF as a potential gene target to manipulate organ-

Box: Questions Outstanding

- Which are the co-factors of Zbtb20 in regulating the cell cycle?
- Are the levels of Zbtb20 involved in maintaining stem cells quiescence?
- Are the levels of Zbtb20 decisive in promoting or blocking cell cycle progression?
- Can Zbtb20 induce cell cycle reentry or cell cycle progression on its own or is it a permissive factor allowing for other genes to exert their function?
specific stem cells in the context of regenerative medicine. For example, it appears that brain stem cells and proliferating hepatocytes down-regulate \textit{Zbtb20} during their activation, while the skeletal muscle stem cells up-regulate \textit{Zbtb20} during activation. Overexpression of \textit{Zbtb20} in plasma cells impairs proliferation \textit{in vitro}, while in the liver a knock-down has such effect on hepatocyte proliferation. The opposing effects on cell activation might be related to the opposing effects of \textit{Zbtb20} on the cell cycle progression and probably depend on interaction with different molecular partners, such as COUP-TFI in cortical progenitors (19), Sox9 in chondrocytes and astrocytes (26, 40). Another important issue whether \textit{Zbtb20} is able to affect the cell cycle directly or rather it acts a permissive factor allowing for other genes to exert their function. These and other outstanding questions need to be answered in order to get a better understanding regarding the role of \textit{Zbtb20} in progenitor cell biology.

\textbf{CONFLICT OF INTERESTS}

There authors declare no conflict of interests exists.

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