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Pfkfb (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase) isoforms display a tissue-specific and dynamic expression during *Xenopus laevis* development

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ABSTRACT

Pfkfb (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase) enzymes are bi-functional enzymes encoded by four different genes (*pfkfb1*, *pfkfb2*, *pfkfb3*, *pfkfb4*) in vertebrates. They are involved in the regulation of glycolysis: they catalyze the synthesis and the degradation of F-2,6-BP (fructose-2,6-bisphosphate), the most potent allosteric activator of phosphofructokinase 1 (Pfk1), a key glycolytic enzyme. By producing F-2,6-BP, Pfkfb enzymes allow glycolysis to proceed, while by degrading F-2,6-BP they block glycolysis. As major regulators of glycolysis, Pfkfb enzymes are involved in cancer: tumor cells have a higher glycolytic rate compared to normal cells, even in the presence of adequate oxygen levels (Warburg effect) and several cancer cell lines express elevated levels of Pfkfb enzymes. Glycolysis is also important for energy and metabolite production in proliferating cells. In embryos, however, the role of glycolysis and the expression of glycolysis regulators remain to be explored. Here, we provide a phylogenetic analysis of Pfkfb enzymes in vertebrates, and we detail the expression pattern of *pfk1*, *pfkfb1*, *pfkfb2*, *pfkfb3*, and *pfkfb4* genes in *Xenopus laevis* embryos. We show that *pfkfb* transcripts expression is overlapping at blastula and gastrula stages and that from neurulation to tadpole stages, they display tissue-specific, complementary and dynamic expression patterns.

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Pfkfb proteins (6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase) are bi-functional homodimeric enzymes with a kinase domain in their N-terminal half and a phosphatase domain in their C-terminal half. By their kinase activity, these enzymes catalyze fructose-2,6-bisphosphate (F-2,6-BP) synthesis from fructose-6-phosphate (F-6-P) and ATP, while with their phosphatase activity, they catalyze the degradation of F-2,6-BP into F-6-P and inorganic phosphate (P_i) (Okar et al., 2001). Fructose-2,6-bisphosphate is an activator of glycolysis and an inhibitor of gluconeogenesis (a scheme of glycolysis is provided in Supplemental Fig. 1). F-2,6-BP is the most potent allosteric activator of phosphofructokinase 1 (Pfk1), the enzyme which catalyses the second irreversible reaction of glycolysis. Since F-2,6-BP levels are tightly regulated by Pfkfb enzymes, these are essential regulators of glycolysis rate, and consequently essential for cell survival and metabolism.

In vertebrates, four different genes encode the four Pfkfb proteins. Each of these enzymes has been originally identified in different tissues in mammals: Pfkfb1 in the liver and skeletal muscle, Pfkfb2 in the heart, Pfkfb3 in the brain, Pfkfb4 in the testis (Rider et al., 2004). However, all four are more widely expressed throughout the adult organism. These four proteins display highly similar kinase and bisphosphatase catalytic cores, but they differ in the flanking regions: this confers a different kinase/phosphatase activity ratio to each isoform (Okar et al., 2001; Cavalier et al., 2012). The kinase/phosphatase activity ratio also depends on post-translational modifications: for instance, Ser32 phosphorylation of the liver enzyme Pfkfb1 by PKA leads to the inactivation of the kinase activity and activation of the phosphatase activity (Rider et al., 2004), while the dephosphorylation of the same residue activates the kinase activity and decreases the phosphatase activity (Okar et al., 2004).

Pfkfb enzymes are overexpressed in different cancer cell lines, like melanoma, prostate, pancreatic and gastric cancer cells, mammary gland malignant cells (Minchenko et al., 2004, 2005a, 2005b; Bobarykina et al., 2006). Interestingly, cancer cells are known to have a higher glycolytic rate compared to normal cells, even in the presence of adequate oxygen levels (Warburg effect) (Warburg, 1956). Moreover, glycolysis is essential for tumour survival and spreading (Bartrons and Caro, 2007). Due to their role in glycolysis regulation, Pfkfb enzymes are important for ensuring the high glycolysis levels in cancer cells. Therefore, strategies allowing a fine-tuned inhibition of glycolysis and of Pfkfbs activity may be used to abolish ATP generation and preferentially kill cancer cells (Pelicano et al., 2006).

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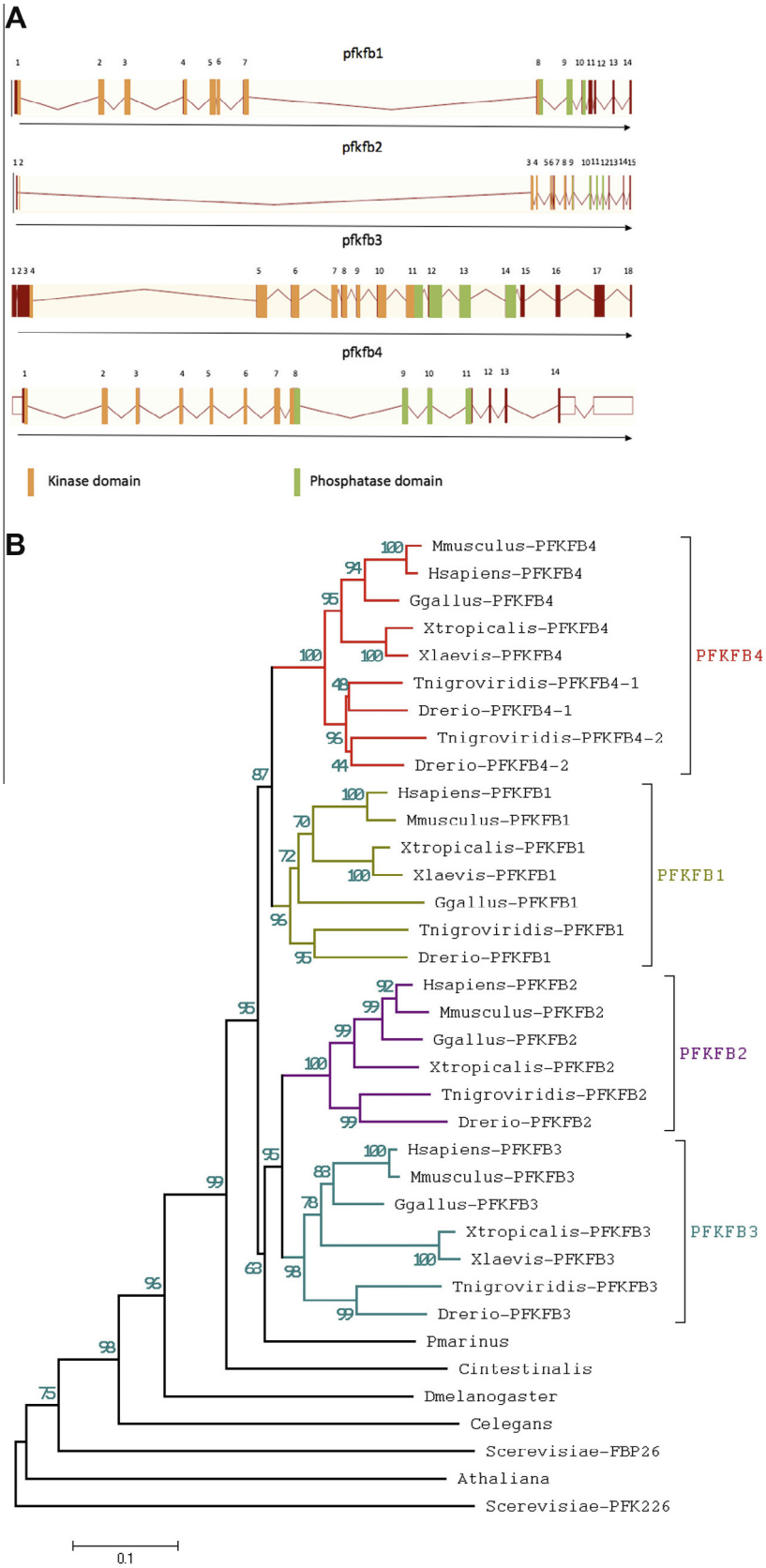

Fig. 1. *Xenopus tropicalis Pfkfb* gene structure and Pfkfb phylogenetic tree. (A) *Xenopus tropicalis* exon–intron gene structure is indicated for *pfkfb* 1–4. *Pfkfb* genes have a similar structure: between 14 and 18 exons are present in each gene and they encode for 470–580 amino acid protein. Exons that form the kinase domain are shown in orange and exons that form the phosphatase domain are shown in green. Exons outside of these two domains are shown in dark red. Each domain is indicated with the corresponding exon number. (B) Phylogenetic analysis of Pfkfb proteins using 12 taxa.

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