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Zebrafish (*Danio rerio*) ecotoxicological *ABCB4*, *ABCC1* and *ABCG2a* gene promoters depict spatiotemporal xenobiotic multidrug resistance properties against environmental pollutants

Leonard Whye Kit Lim [a,*], Hung Hui Chung [a,*], Sairatul Dahlianis Ishak [b], Khor Waiho [b]

[a] Faculty of Resource Science and Technology, Universiti Malaysia Sarawak, 94300 Kota Samarahan, Sarawak, Malaysia
[b] Higher Institution Centre of Excellence (HICoE), Institute of Tropical Aquaculture and Fisheries, Universiti Malaysia Terengganu, 21030, Kuala Neru, Terengganu, Malaysia

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ABSTRACT

Marine organisms are naturally equipped with multixenobiotic resistance mechanisms that are often governed by ATP-binding cassette (ABC) transporter family members. Previous studies focused on the target genes of ABC but little is known about the functionality of their promoter regions. Due to the importance of promoters in ABC transporter gene regulation, we functionally characterized three major xenobiotic transporter promoters of zebrafish, namely *ABCB4*, *ABCC1* and *ABCG2a* via in silico transcription factor binding analysis and in vivo spatiotemporal expression analysis. The former revealed the major functional contributors (such as AP-1, C/EBP beta, HNF-1 and NF-1 TFBSs) towards promoter activity enhancement across four different tissues (liver, muscle, cell cycle and immune cells) where majority of them discovered were liver-specific whereas the latter unearthed the localization of these promoters at liver and intestinal tracts during late embryogenesis (48, 72 and 96 hpf). This study contributes towards future xenobiotic transporter ecotoxicology studies in zebrafish.

1. Introduction

The aquatic environment today is under constant threat of various structurally varied chemicals and these toxicants are posing harm towards living organisms upon exposure. The multixenobiotic resistance (MXR) phenotype is one unique adaptation possessed by aquatic organisms to reduce the adverse effects of both xeno- and endobiotics (Bard, 2000). The MXR mechanism is typically governed by the ATP binding cassette (ABC) superfamily, this transporter gene family is well-known for their efficacy in toxic elimination via ATP driven efflux pumps (Dermauw and Leeuwen, 2014; Higgins, 1992; Jones and George, 2004). ABC proteins participate in numerous vital biological processes ranging from insulin synthesis, toxin excretion, ion trafficking, ribosome recycling, neutral lipid translocation and anticancer drug resistance (Albrecht and Viturro, 2007; Broehan et al., 2013; Ferreira et al., 2014; Kasari et al., 2019; Leonard et al., 2003; Morita and Imanaka, 2012; Popovic et al., 2010; Stefkova et al., 2004).

Xenobiotic transporters orchestrate the cellular import and export of chemicals (Klaassen, 2002). These transporters are also known to provide essential shield for differentiated somatic cells (Schrankel et al., 2020). Interestingly, only 20% of the identified ABC transporters to date are not expressed during early embryogenesis stage (from fertilized egg to gastrulation), indicating the significant roles of ABC transporters in early embryo development especially during the differentiation of ectoderm, mesoderm and endoderm (Schrankel et al., 2020). The major xenobiotic transporter proteins involved during early embryogenesis are the *ABCB4*, *ABCC1* and *ABCG2a* proteins. In sea urchin, *ABCG2a* and *ABCB4* genes were exclusively expressed in the endoderm of hindgut and midgut sections during gut growth initiation whereas the *ABCC1* gene was expressed abundantly and it functions as the homeostatic and defensive agent in all three germ layers (Schrankel et al., 2020). In zebrafish, the *ABCB4* protein serves as embryo's first line of defense shield against toxicants (phase 0), whereas the *ABCG2a* and *ABCC1* proteins act in the third phase of cellular detoxification where they play role in the trafficking of phase I and II metabolic products (Bard, 2000; Fischer et al., 2013; Leslie et al., 2005; Paetzoid et al., 2009).

Although the functional characterization of these xenobiotic transporter genes in zebrafish has been carried out (Kobayashi et al., 2008;

Abbreviations: ABC, ATP-binding cassette; ATP, adenosine triphosphate; PCR, polymerase chain reaction; TFBS, transcription factor binding site.

* Corresponding authors.
E-mail addresses: lwkl1993@gmail.com (L.W.K. Lim), 19010029@siswa.unimas.my (H.H. Chung).

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