Zebrafish

The zebrafish (Danio rerio) is a freshwater fish belonging to the minnow family (Cyprinidae) of the order Cypriniformes.

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Native to the Himalayan region, it is a popular aquarium fish, frequently sold under the trade name zebra danio (and thus often called a "tropical fish" although not native to the tropics). The zebrafish is also an important and widely used vertebrate model organism in scientific research. It is particularly notable for its regenerative abilities, and has been modified by researchers to produce many transgenic strains.

Unfortunately, there are few in vivo model systems for IDH-mutated tumors to study the effects of IDH1 mutations in tumor development.

Gao et al., from the Erasmus Medical Center, Rotterdam, the Netherlands have therefore created transgenic zebrafish lines that express various IDH1 mutants.

IDH1 mutations (IDH1R132H, IDH1R132C and loss-of-function mutation IDH1G70D), IDH1wildtype or eGFP were cloned into constructs with several brain-specific promoters (Nestin, Gfap or Gata2). These constructs were injected into fertilized zebrafish eggs at the one-cell stage.

In total more than ten transgenic zebrafish lines expressing various brain-specific IDH1 mutations were created. A significant increase in the level of D2HG was observed in all transgenic lines expressing IDH1R132C or IDH1R132H, but not in any of the lines expressing IDH1wildtype, IDH1G70D or eGFP. No differences in 5-hydroxymethyl cytosine and mature collagen IV levels were observed between wildtype and mutant IDH1 transgenic fish. To our surprise, we failed to identify any strong phenotype, despite increased levels of the oncometabolite D2HG. No tumors were observed, even when backcrossing with tp53-mutant fish which suggests that additional transforming events are required for tumor formation. Elevated D2HG levels could be lowered by treatment of the transgenic zebrafish with an inhibitor of mutant IDH1 activity.

They have generated a transgenic zebrafish model system for mutations in IDH1 that can be used for functional analysis and drug screening. Our model systems help understand the biology of IDH1 mutations and its role in tumor formation 1 .

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Gao Y, de Wit M, Struys EA, van der Linde HCZ, Salomons GS, Lamfers MLM, Willemsen R, Sillevis Smitt PAE, French PJ. IDH1-mutated transgenic zebrafish lines: An in-vivo model for drug screening and functional analysis. PLoS One. 2018 Jun 28;13(6):e0199737. doi: 10.1371/journal.pone.0199737. eCollection 2018. PubMed PMID: 29953513.

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