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REVIEW ARTICLE

Zebrafish as a model to evaluate peptide-related cancer therapies

Austin Y. Shull[1] · Chien-An A. Hu[2] · Yong Teng[3,4]

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Abstract Peptide-derived drug discovery has experienced a remarkable resurgence in the past decade since the failure of small-molecule modulators to effectively access the large binding surfaces of intracellular protein–protein interactions as well as "undruggable" residues of certain disease-driving proteins. However, the effectiveness of peptide-based cancer therapies is being questioned in light of declines in pharmaceutical R&D efficiency. As a model of whole organism, zebrafish provide a means to develop promising peptide and protein anticancer agents in an informative, cost-effective and time-efficient manner, which also allows for surveying mechanisms of drug action and optimization of drug delivery system. This review highlights the achievements and potential of zebrafish for modelling human cancer and for peptide-based drug discovery and development. Specific challenges, possible strategies and future prospects are also discussed.

Keywords Zebrafish · Cancer models · Drugs · Peptides · Anti-cancer · Strategy and therapy

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✉ Yong Teng
yteng@augusta.edu

[1] Department of Biology, Presbyterian College, Clinton, SC 29325, USA

[2] Department of Biochemistry and Molecular Biology, University of New Mexico Health Sciences Center, Albuquerque, NM 87131-0001, USA

[3] Department of Oral Biology, Georgia Cancer Center of Augusta University, Augusta, GA 30912, USA

[4] Department of Biochemistry and Molecular Biology, Augusta University, 1120 15th Street, Augusta, GA 30912, USA

Introduction

Driven by the exponential growth in information concerning the precise molecular mechanisms dysregulated in cancer as well as the constant pursuit of widening the therapeutic window with treatments that effectively suppress disease progression and minimize adverse side effects, much of the recent efforts in cancer drug development have been directed towards developing highly and specifically targeted therapeutic leads that not only demonstrate ideal pharmacodynamic properties in inhibiting specific disease-driving mechanisms, but also demonstrate desired pharmacokinetic properties needed for providing proper clinical utility and patient tolerability. Based on this therapeutic direction, many academic institutions and pharmaceutical companies have started focusing their labor in developing peptide fragments and biological compounds that can be implemented as therapeutic interventions. In fact, while there are approximately 60 FDA-approved peptide-based therapies in the market as of 2015, there are currently more than 140 peptide therapies undergoing clinical trials and more than 500 therapeutic peptide leads undergoing preclinical assessment (Fosgerau and Hoffmann 2015). Based on this influx of therapeutic peptides into the drug development pipeline, the global market of innovative peptide drugs is expected to increase from US$8.6 billion in 2011 to approximately US$17.0 billion in 2018 (Fosgerau and Hoffmann 2015).

Comparing small molecule and peptide-based therapies

Among the overall initiative of developing "targeted" therapeutics, the efforts of designing specialized inhibitors to

subvert cancer progression have mainly been divided into two classes; chemically synthesized, small molecule compounds and peptide-derived, large molecule compounds (Arkin and Wells 2004; Nilsson et al. 2005; Xie et al. 2016a). Both classes of compounds have their own unique properties that demonstrate a preferential benefit over the other class.

Small molecule compounds

Small molecule compounds, for instance, are typically stable that can easily permeate the cell membrane and perform their derived function within the intracellular compartment. Based on these qualities as well as the relative low cost required to develop and manipulate chemically synthesized compound leads, small molecule compounds have had more recent success in circumventing the pharmacokinetic hurdles needed to make a targeted inhibitor effective, yet tolerable for patients. Nevertheless, these chemical inhibitors are still limited in their molecular specificity, can elicit severe off-target effects, and are generally inefficient at disrupting protein–protein interactions (PPIs) and protein interactomes, that are foundational to specific oncogenic mechanisms, particular including transcription factor binding and certain intracellular cascade signaling mechanisms. This inability to interrupt critical PPIs that promote oncogenic growth has, in fact, left approximately 80% of potential drug targets as "undruggable" based on this limitation (Gongora-Benitez et al. 2013).

Peptide-based compounds

Thus, to counter the therapeutic limitations of specificity for small-molecule chemical inhibitors, large molecule inhibitors, which include protein biologics and peptide-derived compounds, have been developed as specifically arranged amino acid and polypeptide fragments constructed to serve as molecular "mimetics" within the extracellular and intracellular environment (Watt 2006). These mimetics are specifically designed to compete with the native protein domain interactions within the cellular compartments that directly bind together and subsequently elicit particular cascading events that are ultimately responsible for promoting the disease phenotype. Such peptide-based drug designs have provided great potential in overcoming the issues of off-target effects that plague chemically synthesized small molecule inhibitors and establish the therapeutic means of disrupting molecular interactions with immense precision. Nevertheless, the practical issues concerning therapeutic peptides are driven by their relatively large sizes that make them highly impermeable to cell membranes, as well as the poor ability for therapeutic peptides to maintain proper conformation and stability in vivo due to the stress of physiological conditions. Coupled with the economic barrier of peptide-based therapies being immensely more expensive to design and evaluate when compared to small molecule chemical inhibitors, determining the large-scale therapeutic potential of peptide-based therapies has yet to be fully reached.

Recent advancements in peptide therapy development

However, a great deal of effort in recent years has been placed into making these highly specific peptide therapies more stable and permeable to provide more feasible means of using therapeutics peptides in a clinical setting. Such efforts include the development of lipopeptide delivery systems, peptides fused with cell-permeable protein motifs, and conformationally locked small peptide fragments called "stapled" peptides (Xie et al. 2016a; Guo et al. 2010; Walensky and Bird 2014; Teng et al. 2016a, b). Such alterations in therapeutic peptide designs have created the ability to overcome many of the permeability and stability issues that have deterred the potential of peptide therapies.

Nevertheless, the ability to effectively evaluate the potential of therapeutic peptides in a precise and economical fashion still remains to be a critical hurdle. Specifically, one of the major issues regarding preclinical assessment of peptides therapies is relying too heavily on in vitro-based methods on the front end of the development to evaluate certain therapeutic peptide leads. Because many of the obstacles that limit the potential of peptide therapies are caused by the physiological variability of an in vivo environment. Nonetheless, the capabilities of these enhanced peptide therapies have yet to be well evaluated at the in vivo level, with very few having been tested within mouse models. With many of the concerns regarding peptide-based therapies being that of stability within physiological conditions are issues that arise when as well as the associated high cost of developing and assessing the efficacy of these peptide compound leads at the in vivo level, a bottleneck has occurred within the drug development pipeline for determining potentially efficacious compounds that can be advanced into a clinical setting. Based on the spectrum of challenges facing the investigation of peptide-based compound leads, we and other groups have shown that zebrafish (*Danio rerio*) as an ideal model for determining the pharmacodynamic and pharmacokinetic properties of these peptides and overall provided insights into the clinical potential of the peptide-based therapies being investigated (Xie et al. 2016b; Hsieh et al. 2016; Yang et al. 2016).

The power of zebrafish for in vivo screening and evaluation

One proposed measure to alleviate this developmental buildup in evaluating the physiological effects and influences of specific peptide therapies is utilizing zebrafish as an economical, scalable, and well representable in vivo model for human disorders to determine the effectiveness of proposed therapeutic peptide compounds. Within the past decade, zebrafish have emerged as an immensely resourceful and informative model for elucidating specific disease mechanisms involving pathophysiology such as neurodevelopmental disorders (e.g. Parkinson's disease, Alzheimer's disease), muscle disorders such as (e.g. Duchenne muscular dystrophy), metabolic disorders (e.g. diabetes), and malignancies (e.g. leukemias, epithelial cancers) (Lieschke and Currie 2007). Such modeled conditions have been created in zebrafish by means such as forward genetic approaches, which utilize chemical mutagens (e.g. ENU, DEM) to create numerous disease phenotypes to then determine the genotypic root of the conceived phenotypes, or reverse genetic approaches, which utilize oligonucleotide-based manipulation (e.g. morpholinos, zinc-finger nuclease) to disrupt specific gene function and produce specific disease phenotypes (Teng et al. 2010, 2011; Xie et al. 2012). Such approaches have enabled the creation of numerous transgenic zebrafish models, and with 82% of human disease genes having orthologues in zebrafish, many of these transgenic models have served a powerful role in elucidating the progressive steps of human disease development.

Along with the relative accessibility of establishing transgenic models through mutagenic measures to elucidate disease-related mechanisms in zebrafish, several reported studies have utilized the developing zebrafish embryo to determine the mechanistic effects certain therapeutic inhibitors can create during the developmental process of the zebrafish. These particular studies provide opportunity in evaluating which developmental mechanisms, such as limb development, gut development, and blood vessel generation, are specifically disrupted during zebrafish development and offer understanding of how these evaluated inhibitors could be potentially utilized in disrupting relevant pathological mechanisms. One example utilizing this experimental approach came from Ridges et al. (2012) who, through drug screening measures, identified a novel compound called Lenaldekar (LDK) that was able to inhibit the development of immature T cells without disrupting the normal cell cycle progression of other cell type in the zebrafish. Further in vitro cell line and mouse xenograft demonstrated that LDK could be potentially used a therapy for several types of leukemia, including refractory B-ALL and T-ALL. Thus, with these experimental abilities of utilizing zebrafish, the relative affordability of maintaining zebrafish facilities and colonies, and the added ability of visually tracking cellular processes using fluorescent reporter constructs, zebrafish offer several advantages as an in vivo model for evaluating disease states and potential therapeutic interventions for these disease states.

Nevertheless, the utility of zebrafish models has been even further advanced in the field of cancer research by the ability to perform xenotransplantation of human tumor cells into developing zebrafish embryos (Xie et al. 2015). Owing to the transparent and immunoprivileged nature of zebrafish embryos, we have recently established a zebrafish-xenograft model through a critical evaluation of tumor growth and metastatic dissemination using various types of human cancer cells (Xie et al. 2015; Teng et al. 2013; Shao et al. 2013; Hong et al. 2014). By implanting human tumor cell lines into zebrafish embryos 48 h post fertilization (hpf), metastatic potential can be assessed as early as 72 h post injection (hpi) by tracking the fluorescently labeled tumor cells throughout the translucent embryo as they disseminate into other areas and organs within the zebrafish. Several reports have effectively utilized zebrafish xenotransplantation models as a means to evaluate gene functions involved in cancer development and progression with specific examples coming from our group (Xie et al. 2016b, 2015; Teng et al. 2013; Shao et al. 2013; Hong et al. 2014). Hong et al. (2014) evaluated the role of *SHOX2* as a promoter epithelial-to-mesenchymal transition (EMT) and metastasis by creating transgenic breast cancer cell lines that either overexpressed *SHOX2* or silenced *SHOX2* by shRNA and xenotransplanting the engineered cells into zebrafish embryos. As expected, they were able to show that when *SHOX2* was silenced in metastatic MDA-MB-231 cells, MD-MB-231 did not disseminate throughout the zebrafish when compared to control MDA-MB-231 conditions. Comparatively, non-metastatic T47D breast cancer cells engineered to overexpress *SHOX2* showed greater metastatic potential throughout the zebrafish when compared to control T47D cells. In a similar manner, Shao et al. (2013) wanted to determine whether the c-Jun specific E3-ligae, COP1 and the glycogen synthase 3-beta (GSK3β) could cooperatively inhibit tumorigenesis and disrupt metastatic growth. By overexpressing these two proteins in MDA-MB-231 cells and xenotransplanting the transgenic cells in zebrafish, they were able to show that COP1 and GSK3β effectively disrupted metastasis of MDA-MB-231 within the zebrafish when compared to the control cells. We also determined whether the phenotype results from ADP-ribosylation factor 1 (ARF1) knockdown in mouse xenograft models was reproducible in the zebrafish-xenograft model (Xie et al. 2016b). Approximately 200 labeled MDA-MB-231 cells expressing *ARF1* shRNA or control shRNA were microinjected into the perivitelline space of 2

dpf Tg(*kdrl:EGFP*) embryos. Consistent with the findings from mice, loss of ARF1 in the highly metastatic parental breast cancer cells leads to limited spread throughout the zebrafish body compared with the knockdown control cells. These reports, as well as many others, demonstrate the added utility of zebrafish xenotransplantation when evaluating the multi-faceted effects of metastatic tumorigenesis within an in vivo setting.

Based on these elements of the zebrafish xenotransplantation model, in vivo drug/treatment response studies assessing tumor growth and metastasis can be evaluated with relative ease and short timelines in zebrafish when compared to other xenograft models, such as immunocompromised or humanized mice. We have investigated effects of epidermal growth factor (EGF) on breast cancer metastasis using zebrafish model which showing EGF remarkably promoted non-invasive breast cancer to spread to other areas of fish body through blood vessels (Fig. 1a). Given the FDA-approved anticancer drugs have distinct mechanisms of action which may vary in their effects on different types of cancers, our research has repurposed some existing anticancer drugs in the cancer treatment. For example, bevacizumab, a monoclonal antibody with anti-angiogenesis activity, is a medication used to treat many types of cancers. However, it has not applied to the treatment for patients with breast cancer. We have demonstrated that Bevacizumab significantly reduced breast tumor-induced angiogenesis in zebrafish (Fig. 1b). Most recently we have evaluated anti-cancer efficacy of a novel ARF1 inhibitor LM11 using tumor-bearing zebrafish model (Xie et al. 2016b). After excluding drug off-target effects, we identified that 1 μM of LM11 significantly suppressed breast cancer cells to disseminate from the perivitelline cavity to fish body, which suggests that LM11 has strong anti-cancer activities through inhibition of the phenotypes associated with breast cancer metastasis. Therefore, zebrafish can be used to facilitate better understanding of drug anti-disease activities, mechanisms of action of individual agents or combinations at the molecular, cellular, target tissue and even whole organism levels, and provide a means to develop promising preclinical agents.

Evaluating the promise of peptide-based therapies in zebrafish

With a detailed understanding regarding both the technical hurdles in evaluating peptide-based compound leads as well as the particular advances zebrafish provide as an in vivo drug screening/validation model, many researchers have recently started implementing zebrafish in their studies to determine the efficacy and specificity of their therapeutic peptide. This utilization of zebrafish has been especially true for cancer therapeutic studies that have relied on a zebrafish xenotransplantation model to determine whether the peptide-based therapy is preferentially disrupting cancer cell growth and metastatic dissemination without disrupting any of the normal developmental/physiological processes of the zebrafish.

Evaluating a coiled coil peptide-based drug delivery system in zebrafish

One example of implementing zebrafish in peptide-based drug response studies came from Yang and colleagues (2016) who recently demonstrated the targeted ability of a liposomal drug delivery system that utilizes coiled coil peptides. Coiled coil peptide motifs are specific tertiary structural motifs that are in approximately 10% of all protein sequences. These coiled coil motifs can serve in several different biological functions, but one role commonly performed by coiled coil peptides is mediating

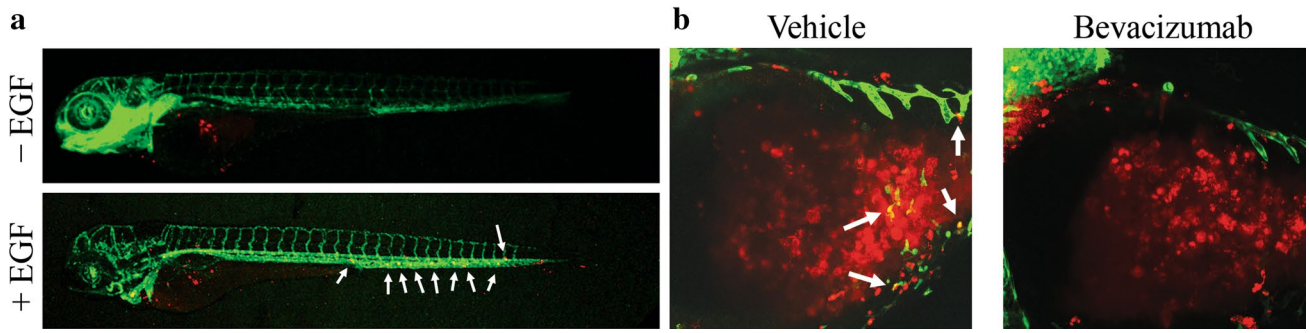

Fig. 1 The examples demonstrate how application of zebrafish cancer model in drug treatment. CM-Dil-labeled T47D cells (*red*) were microinjected into perivitelline space of the Tg(*kdrl:EGFP*) strain at 48 hpf. After confirmation of a visible cell mass at the injection site, the embryos were treated with EGF (**a**) or bevacizumab (**b**) or vehicle for 3 days before confocal analysis. *Yellow* indicates cancer cells (*red*) in fish vasculature (*green*). *White arrows* indicate cancer cells dispersed throughout the fish body in **a** and tumor-induced vessels in **b**

vesicle transport within a cell. Specific examples include the viral entry of HIV into $CD4^+$ T cells by initiating the coiled coil formations of the viral glycoprotein gp41 as well as the merging of SNARE protein subunits through coiled coil formation during neuron vesicle transport. Such use of this coiled coil peptide-based delivery system has enabled efficient transport of several biological modulators, such as siRNAs, proteins, vaccines, and chemical inhibitors, into a cell without having to pass through the harsh endosomal and lysosomal degradation mechanisms that typically succeed endocytic uptake of organic and inorganic materials. This drug-delivery system had demonstrated a great deal of promise in mediating the preferential uptake of non-natural products such as chemotherapeutic agents and mitigating the off-target, cytotoxic effects generally elicited during non-specific delivery of harsh chemical treatments.

Nevertheless, much of the previous evaluation regarding this delivery system has occurred at the in vitro level and the effects of this peptide-based drug delivery in an in vivo model like zebrafish had not been assessed. Because of this experimental void, Yang and colleagues constructed doxorubicin-containing liposomes tethered with coiled coil peptides and used this deliver system to test the capabilities of mitigating cell viability of HeLa cells xenotransplanted in zebrafish while having minimal effect on the health and viability of the zebrafish overall (Yang et al. 2016). Based on their experimental design, they were able to demonstrate that the coiled coil peptide-coupled liposome containing 0.25 mM doxorubicin was able to significantly disrupt HeLa cell growth and metastasis in the zebrafish xenograft models when compared to non-targeting liposomes containing 0.25 mM doxorubicin and freely administered 0.25 mM doxorubicin, which had little effect on HeLa cell proliferation. The potent and targeted disruption of cancer cell growth in the xenograft models when using the coiled coil peptide system is interesting based on the effects achieved when using a dose of doxorubicin five times lower than the acceptable dose typically used in clinical settings. Such as result within an in vivo setting provides further validation of pursuing peptide-tethered liposomal delivery systems as a means of providing both a potent and well-tolerated administering of therapeutic treatment.

Evaluating cell-penetrating inhibitory peptides in zebrafish

Along with peptide based-drug delivery systems and the more established biologic therapies that typically block extracellular signaling components (e.g. immune checkpoint inhibitors, HER2 blocking antibodies), recent efforts have been directed toward designing inhibitory peptide mimetics that can cross the cell membrane and inhibit key intracellular PPIs responsible for the pathological condition. The intended idea of utilizing these designed peptides is to have intentionally designed short peptide sequences that mimic the binding domains of aberrant molecular interactions found in specific disorders to compete with the native molecular interaction and disrupt its disease driving mechanism. This rationale in drug design ideally expands the therapeutic window by enabling increased specificity towards the intended target while concurrently decreasing unintended cytotoxic outcomes triggered by off-target interactions. However, determining the best means for enabling inhibitory peptides to penetrate the membrane barrier while maintaining proper conformational activity is still a critical hurdle for basic biomedical and pharmaceutical scientists to consider when implementing these intracellular mimetics, especially when considering the physiologically dynamic circumstances of in vivo conditions. Thus, zebrafish could be an ideal in vivo for evaluating many of the inquiries that concern cellular penetration, conformational stability, and the overall efficacy of peptide-based therapy.

One example of using zebrafish to determine the effectiveness of a therapeutic peptide is a recent report by Hsieh and colleagues (2016), who designed a therapeutic peptide to disrupt the tumorigenic PPI of the Wnt pathway-related B-catenin/LEF-1 activation. The Wnt pathway is a well-established signaling cascade implicated in driving metastasis of numerous cancers including colon, ovarian, lung, and breast cancer. During Wnt pathway-activation, one of the final downstream events is B-catenin translocating to the nucleus to bind with LEF-1 as a co-transcription factor and initiating transcription of key oncogenes like *MYC, CCND1,* and *BMP4*. Because of the transcriptional response caused by their activation, the interaction between B-catenin and LEF-1 would be an ideal therapeutic target in cancer. However, because of its highly specialized protein domain interaction and its interaction occurring in the nucleus, the B-catenin/LEF-1 axis has previously proven very difficult to directly disrupt in any therapeutic context. With these obstacles existing in the attempt to mitigate B-catenin/LEF-1 signaling, Hsieh et al. engineered a fusion peptide containing a B-catenin/LEF-1 binding domain (derived from the first 76 amino acids of native LEF-1), a cytoplasm-penetrating TAT motif, and a LEF-1 derived nuclear localization sequence (NLS) to effectively transport through both the cell cytoplasm and nucleus in the ultimate attempt to competitively inhibit B-catenin/LEF-1 interaction. After determining that the therapeutic peptide does in fact inhibit B-catenin/LEF1 nuclear interaction and disrupts oncogenic growth of breast cancer cells in vitro, Hsieh and colleagues further evaluated the effectiveness of the peptide by treating zebrafish

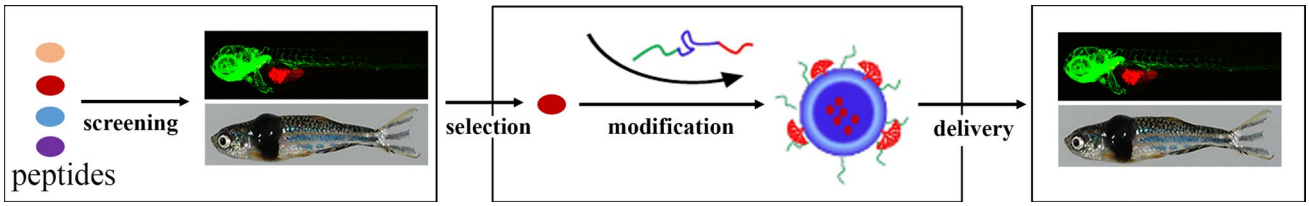

Fig. 2 Schematic representation of the flowchart for chemical peptide-based drug screening and delivery in zebrafish-cancer models

embryos harboring xenotransplanted, GFP-expressing breast cancer cells (MCF7 and MDA-MD-231) with the inhibitory peptide. Based on their experimental design, Hsieh et al. were able to demonstrate the designed mimetic's ability to significantly interrupt tumor cell growth and invasiveness within the xenotransplanted zebrafish after 24 and 48 h, respectively, without causing any apparent toxicological issues in the zebrafish. Collectively, these results helped demonstrate the efficacious nature of utilizing peptide mimetic therapy as well as exhibit the potential and practicality of evaluating the in vivo effects of precisely designed inhibitory peptides within a scalable, economical, highly informative model, and in vivo model, like the zebrafish.

Future directions

As the technical capabilities of both therapeutic peptide development and zebrafish-based cancer and drug screening models continue to independently advance, these technical advances will be able to converge and allow zebrafish-based in vivo modeling to exponentially increase the detailed and timely evaluation of potentially efficacious therapeutic peptide and provide clearer insight into potential clinical success for these evaluated peptides. Many of the experimental designs already established including discovery screens of small molecule inhibitors designed to target specific processes within zebrafish as well as xenotransplantation of transgenic cell lines could be used to evaluate the effectiveness of specifically designed peptides within an in vivo setting. In addition, considering that most of available peptide derived drugs have poor in vivo stability, specificity and selectivity, innovative drug delivery systems with multiple extracellular and intracellular barriers to efficiently and rapidly release the drug at the site of action can be also examined in zebrafish (Fig. 2).

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

Research involving human participants and/or animals Not applicable.

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