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Research review paper

Progress and biotechnological prospects in fish transgenesis

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ABSTRACT

The history of transgenesis is marked by milestones such as the development of cellular transdifferentiation, recombinant DNA, genetic modification of target cells, and finally, the generation of simpler genetically modified organisms (e.g. bacteria and mice). The first transgenic fish was developed in 1984, and since then, continuing technological advancements to improve gene transfer have led to more rapid, accurate, and efficient generation of transgenic animals. Among the established methods are microinjection, electroporation, lipofection, viral vectors, and gene targeting. Here, we review the history of animal transgenesis, with an emphasis on fish, in conjunction with major developments in genetic engineering over the past few decades. Importantly, spermatogonial stem cell modification and transplantation are two common techniques capable of revolutionizing the generation of transgenic fish. Furthermore, we discuss recent progress and future biotechnological prospects of fish transgenesis, which has strong applications for the aquaculture industry. Indeed, some transgenic fish are already available in the current market, validating continued efforts to improve economically important species with biotechnological advancements.

1. Introduction

Transgenic animals are genetically modified organisms (GMOs) with inheritable changes to the genome. The genetic engineering of a transgenic organism (transgenesis) differs from gene delivery because the former involves integration of exogenous DNA (transgene) into the host genomic DNA (Wakchaure et al., 2015; Mclean and Laight, 2000), generating a modified gamete, whereas the latter is simply the insertion of a gene into a cell. Clearly, these intentional in vitro genomic alterations in transgenic animals are distinguished from the spontaneous mutations that naturally occur during biological evolution (McColl et al., 2003). It is also important to highlight the difference between gene delivery methods and transgenesis techniques. Gene delivery methods are ways to get the sequence of interest into the target cell; so, these methods are not responsible for genomic integration itself although it can occur as a consequence. For example, microinjection and electroporation are gene delivery methods. If the DNA sequence is injected with sticky ends, integration into genomic DNA may randomly occur but the microinjection and electroporation were not the responsible for that. While plasmid, viral vector, TALEN, and CRISPR/Cas, on the other hand, are transgenesis technique because each technique allow genomic integration. Considering CRISPR/Cas for example, Cas enzyme promotes the cut in DNA in the region where genomic integration will take place. It is directly involved in the sequence of events that will culminate in genomic integration of a DNA transgene.

Transgenesis has improved our knowledge of biological and molecular processes in numerous organisms. In addition to the theoretical advantages in increasing our understanding of physiological mechanisms, animal transgenesis has broad applications across various industries. The enhancement or removal of particular traits can improve livestock productivity, for example (Saxena and Jha, 2013; Collares et al., 2005). Additionally, transgenic animals are useful as bioreactors that produce pharmaceutical substances and other products important to human health (Mclean and Laight, 2000; Santos et al., 2016).

Various techniques have been developed to perform gene delivery, including electroporation and pronuclear microinjection, and different methodologies of transgenesis have also been generated, for example infection using viral vectors and CRISPR/Cas system. However, even

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with recent technological advances, these methods have achieved limited success due to low efficiency, high cost, and unpredictability (even site-directed genomic edition technologies such as CRISPR/Cas can present off-target cut). The generation of mosaic animals is common, as the interaction of exogenous DNA with host genomes exhibits considerable variability. To address these issues, the use of spermatogonial stem cells (SSCs) as targets for genetic modification has become increasingly attractive because they offer a more straightforward route for transgenesis (Lacerda et al., 2010; Lacerda et al., 2014; Tonelli et al., 2016). Modified SSCs are transplanted into recipient gonads to develop and generate transgenic gametes (Tonelli et al., 2017). Using transgenic gametes to fertilize normal oocytes is hypothesized to improve transgenesis efficiency (Collares et al., 2005), because one SSC gives rise to numerous spermatozoa it could potentially transfer genetic modifications to the next generation rapidly.

In fish, SSC modification is a simple and non-expensive procedure (Tonelli et al., 2016; Tonelli et al., 2017). Indeed, fishes are attractive models for genetic manipulation; they offer several advantages, including exogenous proteins that can be efficiently modified post-translation, strong tolerance to environmental change (e.g. pH, temperature, rearing system), and (in some species like the Nile tilapia) a fast life cycle, reaching sexual maturity quickly (Nkhoma and Musuka, 2014). Here, we review the history of fish transgenesis, common transgenic techniques, SSC transplantation's potential to revolutionize fish transgenesis, the biotechnological applications of transgenic fish, and what is in store for the future.

2. Transgenic fish: a brief history

2.1. Genetic engineering in the 60s

Mature organisms comprise differentiated cells (forming tissues) and undifferentiated stem cells that retain proliferating potential. The latter can differentiate when needed to ensure tissue homeostasis. Differentiated cells were considered more stable, lacking the ability to undergo functional changes. However, in the 60s, research demonstrated that differentiated cells were more plastic than previously thought; after removal from its originating tissue, a differentiated cell could interact with and adapt to a new microenvironment. It was possible, for example, to generate tadpoles from enucleated, unfertilized *Xenopus* eggs after inserting a nucleus from intestinal epithelium cells of juvenile frogs (Gurdon, 1962). This landmark study demonstrated that genes are not lost or changed during cell differentiation but rather are differentially expressed. Furthermore, cells isolated from the *Drosophila* genital disk were observed to generate wings, legs, and head after transplantation into new ectopic sites (Ursprung and Hadorn, 1962), indicating that cells originally fated for genital structures gave rise to different organs (Hadorn, 1966). During this decade, successful DNA-delivery methods were developed, allowing researchers to transfect D98S human cell lines with various genes of interest (Szybalska and Szybalski, 1962). In 1965, Arber discovered restriction enzymes, able to slice DNA at specific sites (Arber, 1965), and two years later, Zimmerman et al. (1967) characterized DNA ligase from *Escherichia coli* cellular extracts, opening the possibility of artificially binding disparate DNA ends into a single molecule (Fig. 1). These breakthroughs marked the advent of recombinant DNA technology, facilitating the creation of DNA molecules that contain sequences from separate species.

2.2. Animal transgenesis in the 70s

The 70s saw the first transgenic organism created using the recombinant DNA technology (Fig. 1). Cohen et al. (1972) demonstrated that DNA plasmids act as effective gene carriers, especially when associated with antibiotic-resistance genes. Plasmids delivered to bacteria (*E. coli*) could incorporate and replicate genetic information from different species (Cohen et al., 1973). One year later, the SV40 viral DNA was microinjected into a pre-implantation mouse blastocyst to create the first transgenic animal (Jaenisch and Mintz, 1974). Subsequently, retroviruses were used as the delivery vehicle for foreign DNA germ-line transmission (Jaenisch et al., 1975).

New evidence pertaining to cell plasticity continued to mount during this decade. Selman and Kafatos (1974) proposed the term "transdetermination" to describe the conversion of cuticle-producing cells to salt-secreting cells during the larval metamorphosis of the silkworm to the adult moth. In their seminal experiments on quail and chicken, Le Lievre and Le Douarin (1975) demonstrated that cell fate is dictated by the microenvironment during embryonic development, rather than by the cell's original location. Transplanted quail cells could participate in chicken development due to inherent similarities, but they differed enough in morphology that they could be tracked throughout the process. The results showed that cells explanted from the neural crest adapted to new destinations, generating bone, cartilage, and connective tissue. Following these developments, gene transfer methods became increasingly common, with chromosomes used as gene delivery vehicles by the mid-70s (Willecke and Ruddle, 1975) (Fig. 1).

2.3. Animal transgenesis in the 80s

The 80s was characterized by greater focus on using mRNA to produce foreign proteins in animals. Microinjection of rabbit globin mRNA into murine cells resulted in successful translation (Bravo and Celis, 1980). Furthermore, rabbit proteins were produced in both adult mice and their offspring when relevant genes were microinjected into murine zygotes (Wagner et al., 1981), providing evidence of genomic integration. One year later, researchers developed a mouse expressing a metallothionein-controlled growth hormone gene (GH) and demonstrated that the transgene's influence caused more rapid growth (Palmiter et al., 1982). Further application of microinjections technique resulted in the generation of transgenic rabbits, pigs, sheep (Hammer et al., 1985), and fish (see Section 2.4). During the late 80s, bioreactor animals (typically transgenic mice) were used to produce a variety of milk enriched in proteins of interest, such as ovine β-lactoglobulin (Simons et al., 1987) and human tissue plasminogen activator (Gordon et al., 1987) (Fig. 1).

2.4. Fish transgenesis in the 80s

Table 1 provides an overview of fish transgenesis starting from its initial development in the 80s. Mclean and Talwar (1984) microinjected cloned DNA into newly fertilized rainbow trout (*Oncorhynchus mykiss*) eggs and observed transgenesis in 5% of the resultant fish. Subsequently, Zhu et al. (1985) microinjected pBPVMG-6 plasmid (metallothionein promoter fused with human growth hormone gene) into fertilized goldfish (*Carassius auratus*) eggs and demonstrated that the animals carried the injected sequence even 50 days later, indicating successful integration into the genome. The same sequence transmission was then reproduced in common carp (*Cyprinus carpio*) and rainbow trout (Mclean et al., 1987). Interest in improving commercial fish production led to attempts at expressing GH in transgenic fish. Eventually, human GH gene was successfully transferred with microinjection into the fertilized eggs of channel catfish (*Ictalurus punctatus*) (Dunham et al., 1987) and Nile tilapia (*Oreochromis niloticus*) (Brem et al., 1988) (Table 1).

Why working with fish is advantageous to achieve transgenesis? First of all, it should be mention that aquiculture is an important field for world economy. Fishery products exports increased from $8 billion in 1976 to $148 billion in 2014 (FAO, 2016) and through transgenesis it is possible to improve food conversion ratios, for example increasing growth rate and reducing animal food intake. It is also possible to remove allergenic substances in seafood which could increase it

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