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Sonic The Hedgehog to the rescue?

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'When Dr Eggman was hatching his plans for a global takeover, there was one little thing he didn't count on – Sonic The Hedgehog! Our blue hero zips, flips, and spins through the levels at lightening speed to collect the Chaos Emerald and restore World Order' (game description from the Sonic website).[1] The Sonic video game debuted in 1991 as a platform to illustrate the new 16-bit graphic Sega Genesis system. This new system had (for that time period) faster graphics and more realistic animation and sound. The success of Sonic motivated further improvements in animation, graphics and speed within the video game industry. Today, Sega is a multinational corporation with assets in excess of 450 billion ¥; much of this growth resulted from the success of their little blue hedgehog.[2]

The discovery of the Sonic Hedgehog gene (SHh) came shortly after the debut of the video game. The gene was discovered in a cDNA library search for sequences homologous to the *Drosophila melanogaster* Hedgehog gene, and it was named after the Sega character.[3] The SHh signaling cascade is complex and still not completely understood. Triggers for SHh expression have not been fully elucidated, and function of the pathway has been described mainly in the context of developmental defects caused by mutations. The known participants include SHh, a secreted protein that undergoes extensive post-translational modification before secretion from a primary cell, and several proteins in receptor cells: Patched, the cellular receptor; Smoothened, an intracellular signaling protein released to function after SHh–Patched binding; and three Gli proteins, zinc-fingered proteins that induce expression of a large number of genes after activation by Smoothened. Abnormalities in SHh signaling have been associated with several genetic syndromes, including holoprosencephaly, Smith–Lemli–Opitz syndrome and Gorlin's syndrome. Overactivity of the pathway in post-natal life causes several cancers, including breast, basal cell, rhabdomyosarcoma, glioblastoma and osteosarcoma (for more extensive review, see Cohen[4] and Villavicencio *et al*.[5]).

In a recent *Nature Medicine* report, Kusano *et al*.[6] added to the growing body of literature on SHh function. They documented SHh activity in ischemic myocardium using a mouse coronary ligation model. The authors used gene transfer technology to expand on this observation. In cardiac fibroblast cultures, SHh overexpression increased Patched and Gli expression and induced production of angiogenic factors. Injection of the SHh plasmid into the ischemic or infarcted zone *in vivo* led to an increase in capillary density and collateral blood vessel formation, and a decrease in fibrosis and apoptosis. The overall effect was an improvement in cardiac function with either ischemia or infarct models. The authors suggested that further development of these findings could lead to a new gene therapy approach for acute or chronic myocardial ischemia.

The findings by Kusano *et al*. come on the heels of disappointing clinical trial results that failed to show benefit after angiogenic growth factor gene therapy.[7,8] Preclinical work in animal models and early uncontrolled clinical trials gave encouragement to the possibility that growth factor gene therapy might provide an alternative for patients who had failed conventional options. Speculation on the lackluster results from the placebo-controlled clinical trials has centered on the limited effects that could be achieved from overexpression of a single growth factor for a process as complex as angiogenesis. From this speculation, the field shifted to more comprehensive approaches for angiogenesis induction, either by stem cell transplantation or by hypoxia-inducible factor-1α gene transfer.[9,10] Kusano *et al*. presented another option. If the hypothesis is correct that growth factor gene therapy failed because insufficient cellular or tissue factors were mobilized to produce durable blood vessels, then advantages of the Kusano approach are the complexity and far reaching effects of the SHh signaling cascade. A principle danger of this approach is the possibility of non-target gene transfer, particularly with a gene family connected to several cancers. In that regard, an advantage to the Kusano approach is the use of a DNA vector. The literature on biodistribution of DNA vectors after myocardial injection is limited to a single report,[11] but that report showed that gene expression only occurred in the target myocardium. Even in the target, expression was limited to a few weeks duration. This is certainly a situation where viral vectors would seem inappropriate, with the possibilities of widespread gene transfer or long-term expression for some viral vectors. Fundamental to this or any gene therapy approach is the need for a thorough understanding of the physiology around the transgene, in this case the very complex SHh signaling cascade. The Kusano paper is an important step in the direction of achieving that goal. Also fundamental to the field of angiogenesis gene therapy is the need to understand the disappointing placebo-controlled clinical trial results in the context of several animal studies that showed improved collateral blood flow and myocardial function after growth factor gene transfer.

In the end, we can hope that SHh gene will do for angiogenesis gene therapy what the Sonic Hedgehog game did for Sega and the field of video games. The Sega game motivated a leap forward in technology and contributed to growth and success of the parent company. Gene therapy continues to need this type of unqualified success. Hopefully, 10 or 20 years from now, we will be able to look back on the SHh gene transfer experience in the same way that we now see the Sonic Hedgehog video game experience. It will have propelled the technology forward and led to bonafide clinical successes. ■

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