



## Cover Story

## Enhanced regeneration capacity of cardiac stem cells by TAT-Hsp27



Endogenous cardiac stem cells (CSCs) residing in the adult myocardium are known to retain the ability to differentiate and regenerate all cardiac cells. Clinical translation of such cardiomyogenic potential, however, has been disappointing. The critical factor limiting the therapeutic benefits of CSC therapeutics appears to be poor cell survival, resulting in poor engraftment of transplanted cells in the infarcted myocardium [1]. More than 90% of donor cells are reported to die within 3 days after delivery in the hypoxic and inflammatory environment in the host myocardium. Thus, successful engraftment of CSCs requires a strategy for preventing massive cell death after transplanting in the infarcted heart.

A few approaches have been tried to enhance the cell survival during the critical period after delivery. Cells have been preconditioned *ex vivo* with chemicals, cytokines, growth factors, heat shock, or ischemia to increase the resistance of donor cells against oxidative stress. Their cytoprotective effects, however, are only transient and sustain for less than 2 h, which is far too short for the meaningful increase in cell survival and engraftment in clinical settings. Another approach has been genetic modification of donor cells to overexpress prosurvival factors. This approach, like any other gene delivery techniques, suffers from the same difficulty in controlling the expression level and duration of the transduced prosurvival gene. More importantly, a low intracellular transduction efficiency of a non-viral method necessitates the use of viral vectors that are associated with a risk of insertional mutagenesis and unexpected immune response in humans. In this issue, Dr. Young-Il Yang and his colleagues describe direct *ex vivo* delivery of prosurvival factor into CSCs using a TAT protein transfer domain (PTD) [2].

In the heat shock protein (HSP) family, a small 27-kDa HSP (Hsp27) plays a broad range of anti-oxidant and anti-apoptotic roles in a variety of ischemic and inflammatory diseases [3]. Hsp27 is promptly expressed in response to oxidative stress and suppresses both upstream and downstream apoptotic factors substantially, indicating its broad and powerful cytoprotective ability. The Yang group successfully introduced a recombinant Hsp27 into CSCs through a TAT PTD in dose- and time-dependent manners. Transduced CSCs with Hsp27-TAT fusion protein attained increased anti-oxidative and anti-apoptotic properties via suppressing intracellular reactive oxygen species production, mitogen-activated protein kinase signaling pathway, and caspase activation. This leads to a meaningful increase in cell survival and engraftment of CSCs in the acutely infarcted myocardium, resulting in enhanced cardioprotective benefits of CSCs.

The study by the Yang group presents a few interesting observations. First, the intracellular transduction of Hsp27 into CSCs by TAT PTD reached a maximum level in less than 1 h and sustained its biologic stability for 3 days without any cytotoxic effect. The CSCs transduced with

TAT-Hsp27 rapidly upregulated the expression of endogenous Hsp27 in response to oxidative stress, which was comparable to that of non-transduced CSCs, indicating that an inherent cytoprotective mechanism of transduced CSCs was maintained. But, endogenously upregulated Hsp27 was not as adequate to resist sustained oxidative-induced cell damage. This highlights the importance of exogenous transduction of a prosurvival factor, Hsp27. Second, intracellular transduction of TAT-Hsp27 did not influence renewal and cardiomyogenic differentiation potentials of CSCs. Moreover, their cardioprotective benefits, both anti-inflammatory and anti-apoptotic properties, were not changed. The TAT-Hsp27 transduced CSCs showed an additional anti-apoptotic benefit that suppressed the release of caspase 3/7 in the infarcted hearts. This may be due to the increased engraftment rate of CSCs transduced with TAT-Hsp27 instead of the anti-apoptotic effect of TAT-Hsp27.

Suboptimal cell survival and engraftment appears to be one of the major hurdles for successful myocardial regeneration with stem cell therapy. The encouraging, although small, therapeutic benefits of CSCs observed in clinical trials have occurred despite the low rates of cell survival and engraftment [3]. Taking full advantage of the potential of myocardial regenerative therapy entails development of reliable strategies for improving long-term cell engraftment. The *ex vivo* treatment of CSCs with TAT-Hsp27 appears to be such a strategy, and we all hope that further studies on this lead to successful clinical translation in the not too distant future.

## References

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