Elabela identified as potential hormone for regenerative medicine

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Scientists from the Institute of Medical Biology (IMB) of Agency for Science, Technology and Research (A*STAR), in Singapore, have discovered that the recently-identified hormone ELABELA is critical in promoting the growth of human embryonic stem cells (hESCs), suggesting its potential as a target for applications in tissue engineering and regenerative medicine. The study was done in collaboration with A*STAR's Institute of Molecular and Cell Biology (IMCB) and Genome Institute of Singapore (GIS).

Clinical treatment has seen a paradigm shift towards regenerative medicine in the past decade, in which new cells can restore tissue and organ function by repairing or replacing malfunctioning cells and promoting repair. This departs radically from the past approach of removing damaged cells surgically and using pharmaceutical therapies to mitigate the symptoms, and eliminates the need for organ replacement. With the promising discovery of hESCs and induced pluripotent stem cells (iPSCs) as a way of generating new cells, regenerative medicine appears to be increasingly feasible. However, much remains unknown about the underlying mechanisms of hESCs, and as such, their widespread adoption in regenerative medicine still remains to be seen.

So far, only a few growth factors for hESCs have been discovered. In a ground-breaking study, IMB has now identified ELABELA as necessary for hESCs to self-renew and differentiate, making it a potential target to stimulate hESC growth, and ensuring its stability for use in regenerative medicine. It was found that genetically deleting ELABELA or inhibiting

it with a neutralizing antibody resulted in compromised hESC growth, the loss of pluripotency, and increased cell death. This discovery points to a new role for the ELABELA hormone, which was previously known for its role in early blood vessel and heart development.

IMB's scientists further discovered that ELABELA promotes hESC growth through activating the indispensable PI3K/AKT/mTORC1 pathway, known to regulate cell growth and viability, by promoting cell cycle progression and optimal protein translation. Prior to this, the PI3K/AKT pathway was known to be important for the growth of hESCs, but which endogenous growth factor was driving this effect was not clear.

By activating this pathway, ELABELA also protects the hESCs, and therefore presumably early human embryos, against the intrinsic cell death (apoptosis) pathway which is activated by a variety of cellular and environmental stresses. Given the high susceptibility of hESCs to spontaneous apoptosis and differentiation, ELABELA not only enhances their growth, but also performs the critical function of ensuring their survival.

In regenerative medicine, a key problem is ensuring the stability and survival of hESCs for future differentiation and transplantation. IMB's discovery implies that clinicians and scientists can target and manipulate ELABELA in order to ensure optimal hESC growth during scale-up of cell production for clinical applications, thus making regenerative medicine cheaper and more accessible, and increasing the chances of successful cell replacement.

In addition, hESCs and human pre-implantation embryos are known to be very prone to stress. First author Dr Lena Ho conjectures, "Given ELABELA's effectiveness in protecting them against cellular stress, our findings could have a profound effect on understanding how human pre-

implantation embryos naturally survive after fertilization, with potential applications in fertility clinics."

Corresponding author and IMB/IMCB Senior Principal Investigator Dr Bruno Reversade, whose team discovered ELABELA two years ago, said, "I foresee significant and immediate applications of our discovery, because ELA and its cell surface receptors are readily druggable and have tangible clinical indications."

Professor Birgit Lane, Executive Director of IMB, stated, "This discovery underscores the continued importance of basic research in laying the foundation for clinical applications, and it is very gratifying to see such impact emerging from innovative research, with long-term translational potential for improving healthcare."

More information: "ELABELA Is an Endogenous Growth Factor that Sustains hESC Self-Renewal via the PI3K/AKT Pathway." DOI: dx.doi.org/10.1016/j.stem.2015.08.010

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