California Institute for Regenerative Medicine

Screening the mammalian extracellular proteome for regulators of embryonic human stem cell pluripotency.

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Public Summary:

Scientific Abstract:
Approximately 3,500 mammalian genes are predicted to be secreted or single-pass transmembrane proteins. The function of the majority of these genes is still unknown, and a number of the encoded proteins might find use as new therapeutic agents themselves or as targets for small molecule or antibody drug development. To analyze the physiological activities of the extracellular proteome, we developed a large-scale, high-throughput protein expression, purification, and screening platform. For this study, the complete human extracellular proteome was analyzed and prioritized based on genome-wide disease association studies to select 529 initial target genes. These genes were cloned into three expression vectors as native sequences and as N-terminal and C-terminal Fc fusions to create an initial collection of 806 purified secreted proteins. To determine its utility, this library was screened in an OCT4-based cellular assay to identify regulators of human embryonic stem-cell self-renewal. We found that the pigment epithelium-derived factor can promote long-term pluripotent growth of human embryonic stem cells without bFGF or TGFbeta/Activin/Nodal ligand supplementation. Our results further indicate that activation of the pigment epithelium-derived factor receptor-Erk1/2 signaling pathway by the pigment epithelium-derived factor is sufficient to maintain the self-renewal of pluripotent human embryonic stem cells. These experiments illustrate the potential for discovering novel biological functions by directly screening protein diversity in cell-based phenotypic or reporter assays.

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