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Small molecule lineage-specification of pluripotent human embryonic stem cells and its implication for the future of stem cell therapy

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Pluripotent human embryonic stem cells (hESCs) have unlimited expansion ability and unrestricted intrinsic plasticity for differentiation into all somatic cell types in the human body, holding tremendous potential for restoring tissue and organ function. However, realizing the developmental and therapeutic potential of hESCs has been hindered by the current state of the art for generating functional cells through multi-lineage differentiation of pluripotent cells, which is uncontrollable, inefficient, instable, highly variable, difficult to reproduce and scale-up. Developing novel strategies for the intrinsic developmental programs of pluripotent hESCs to systematically unfold in a lineage-specific manner is vital to harnessing the power of hESC biology for cell-based therapy. To tackle the shortcomings in conventional approaches, we have resolved the elements of a defined culture system necessary and sufficient for sustaining the epiblast pluripotence of hESCs, serving as a platform for de novo deviation of clinically-suitable hESCs and effectively directing such hESCs uniformly towards specific functional lineages. We found that pluripotent hESCs maintained under the defined culture conditions can be uniformly converted into a specific lineage by small molecule induction. Retinoic acid was found to induce the specification of neuroectoderm direct from the pluripotent state of hESCs and trigger progression to neuronal progenitors and neurons efficiently. Similarly, nicotinamide was found to induce the specification of cardiomesoderm direct from the pluripotent state of hESCs and trigger progression to cardiac precursors and cardiomyocytes efficiently. To uncover key regulators, microRNA expression profiling using microarrays was used to identify novel sets of human embryonic development initiating miRNAs upon lineage specification direct from the pluripotent stage of hESCs. A unique set of pluripotence-associated miRNAs was down-regulated, while novel sets of distinct cardiac- and neural-driving miRNAs were up-regulated in lineage-specific differentiation of pluripotent hESCs by small molecule induction, including silencing of the most prominent pluripotence-associated hsa-miR-302 family and a drastic expression increase of Hox miRNA hsa-miR-10 family upon neuroectoderm induction by RA. This technology breakthrough enables well-controlled generation of a large supply of cardiac/neural lineage-specific progenies across the spectrum of developmental stages direct from the pluripotent state of hESCs with small molecule induction for cell-based therapies. To date, lacking of clinically-suitable human neuronal/cardiomyocyte cell sources has been the major setback in developing cell-based therapies for restoring the damaged or lost nerve/myocardium tissues in CNS/heart diseases. The availability of human neurons/cardiomyocytes in high purity and large quantity with adequate neurogenic/cardiogenic potential will accelerate the development of effective cell-based therapies against CNS/heart diseases

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