Editorial

Stem Cell INVESTIGATION

Discovery of a new role for the p53 family in the onset of mesendodermal differentiation of embryonic stem cells

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Embryonic stem cells (ESCs) are derived from and closely related to the pluripotent cells of the early mammalian embryo. ESCs are able to re-enter embryonic development to populate the entire embryonic body once introduced into the blastocyst. Furthermore, such capacity of ESCs for unrestricted differentiation is possible both *in vivo* and *in vitro*, providing an excellent platform for studying early mammalian embryogenesis (1). Moreover, because of these remarkable properties, ESCs and induced pluripotent stem cells, which bear essentially the same biological properties as ESCs (2), are regarded with great promise for use in regenerative medicine as sources of numerous transplantation-competent cell types (3). However, the directed differentiation required to generate any specific cell type from these cells is much more difficult relative to inducing the full repertoire of differentiated cells; therefore, understanding the molecular basis of each specific differentiation pathway is crucial for efficient generation of a desired differentiated cell type.

In the January issue of *Cell Stem Cell*, Wang *et al.* unequivocally demonstrated that p53 family proteins function as key regulators for the onset of ESC differentiation towards mesendodermal cells (4). Involvement of p53 in early embryogenesis has been previously suggested from analyses of *Xenopus* embryos in which depletion of p53 renders the embryos refractory to gastrulation (5). However, the involvement of *p53* in mammalian embryogenesis remains controversial because p53 homozygous knockout mice develop normally; albeit they are prone to tumorigenesis (6). This apparent discrepancy may be explained by the presence of p63 and p73 proteins, whose DNA sequence recognition specificities and other biochemical properties are highly similar to those of p53 (7). Moreover, expression profiles of these three genes significantly overlap in undifferentiated and differentiation-induced ESCs as well as in early embryos, further raising the probability of functional redundancy whereby p63 and/or p73 compensate for p53 in the p53-null background. Therefore, Wang *et al.* generated triple knockout ESCs and clearly demonstrated that loss of all three genes prevents ESCs from differentiating into mesendodermal cells. Indeed, through chimera analyses they demonstrated significant bias in the cell fate of triple knockout ESCs, with a neuroectodermal cell fate favored and the contribution to endodermal cells reduced.

Subsequently, Wang *et al.* explored the molecular mechanisms by which p53 family proteins contribute to mesendodermal differentiation of ESCs. The Nodal-Smad2/3 pathway is known to drive mesendodermal differentiation during gastrulation (8); therefore, they initially considered the possibility of a direct link between p53 family proteins and Smad2/3. However, biochemical analyses revealed no significant interactions or commonality in genomic binding sites between them. Instead, they identified two classes of genomic binding site for Smad2/3, one being dependent on the presence of the p53 family and

the other being independent. The former Smad2/3 binding sites are enriched in mesendodermal genes. Furthermore, transcription factor motif analyses revealed that the binding motif for Tcf transcription family proteins, which function together with β-catenin as downstream effectors of Wnt signaling (9,10), is enriched near most of the p53 family dependent, but not the p53 family independent, Smad2/3 binding sites. They then showed that inhibition of Wnt signaling not only diminished the binding of Tcf, but also the binding of Smad2/3 to these sites. Likewise, inhibition of nodal signaling resulted in simultaneous reductions of Tcf and Smad2/3 binding on these sites. Finally, they demonstrated that p53 dependence of these Smad2/3 binding sites is explained by the p53-mediated potentiation of *Wnt3* transcription. Indeed, they clearly demonstrated that the p53 dependence of Smad2/3 genomic binding was nullified by the addition of Wnt3 to the culture medium.

In summary, Wang *et al.* demonstrated that p53 family proteins unequivocally contribute to mesendodermal specification during differentiation of ESCs and elegantly determined the molecular basis of this cellular differentiation in which p53-Wnt-Tcf3 and Ndal-Smad2/3 pathways are involved in an interdependent manner. Although the molecular pathway revealed by Wang *et al.* corresponds to a very early step in the efficient preparation of transplantation-competent cells, such as insulin-producing cells, we consider that explicit understanding of the biological principle underlying mesendodermal specification, as reported by Wang *et al.*, provides a firm milestone towards this goal.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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