Sprouty4 is a critical negative regulator of the pluripotent state in embryonic stem cells
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Published on 23 Oct 2010

A hallmark feature of embryonic stem (ES) cells is their ability for self-renewal to maintain pluripotent. ES cells can be derived and maintained independently of serum and cytokines using compounds that negatively regulate signalling pathways. Here, we report that innate Sprouty4 (Spry4) action deploys a similar strategy by inhibiting specific signalling cascades. We find that Spry4 is highly enriched in ES cells and is likewise confined to the inner cell mass of mouse blastocysts. Chromatin immunoprecipitation and overexpression assays validate Spry4 as a direct target of the pluripotency factor Nanog. Constitutive Spry4 expression increases expression of important stem cell regulators, thus lodging ES cells in an uncommitted state. Importantly, sustained Spry4 expression voids the need for chemical inhibition under 3i culture condition. Conversely, expressing a dominant negative Spry4 mutant sensitizes ES cells to differentiation inducing endoreduplication and adopting a preferential trophectoderm differentiation. Altogether, our results show that in ES cells Spry4 is critically suppresses differentiation. In order to remain pluripotent an ES cell uses the Spry4 activity to curtail ES cell signalling pathways.