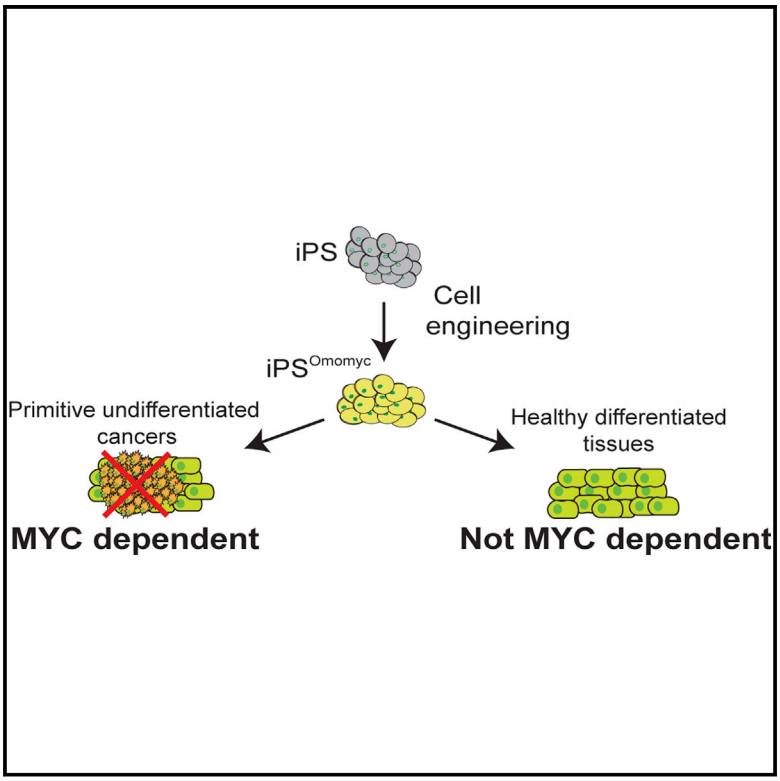
Report

Cell Reports

A Cell Engineering Strategy to Enhance the Safety of Stem Cell Therapies

Graphical Abstract



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In Brief

The risk of malignancies arising from iPSC-derived tissues is a critical concern in stem cell therapies. Oricchio et al. report an iPSC engineering strategy that exploits cancer dependence on MYC and can be activated should a malignancy arise. They further report that MYC blockade disrupts a cancer-specific feed-forward program centered on the role of PKM2 in cancer metabolism and its ability to modulate gene expression via histone H3 phosphorylation.

Highlights

Cancer and normal tissues derived from iPSCs differentially depend on MYC

MYC sustains tumor-specific metabolic and chromatin changes in iPSC-derived tumors

Engineering iPSCs with dominant-negative MYC is a therapeutic fail-safe strategy

Oricchio et al., 2014, Cell Reports 8, 1677–1685
September 25, 2014 ©2014 The Authors
http://dx.doi.org/10.1016/j.celrep.2014.08.039

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A Cell Engineering Strategy to Enhance the Safety of Stem Cell Therapies

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http://dx.doi.org/10.1016/j.celrep.2014.08.039

SUMMARY

The long-term risk of malignancy associated with stem cell therapies is a significant concern in the clinical application of this exciting technology. We report a cancer-selective strategy to enhance the safety of stem cell therapies. Briefly, using a cell engineering approach, we show that aggressive cancers derived from human or murine induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) are strikingly sensitive to temporary *MYC* blockade. On the other hand, differentiated tissues derived from human or mouse iPSCs can readily tolerate temporary *MYC* inactivation. In cancer cells, endogenous MYC is required to maintain the metabolic and epigenetic functions of the embryonic and cancer-specific pyruvate kinase M2 isoform (PKM2). In summary, our results implicate PKM2 in cancer's increased MYC dependence and indicate dominant MYC inhibition as a cancer-selective fail-safe for stem cell therapies.

INTRODUCTION

Tissues derived from pluripotent stem cells (PSCs) cells have great potential in regenerative medicine and can, in principle, replace any differentiated tissue (Hanna et al., 2007; Takahashi and Yamanaka, 2006). Recent successes include the generation of retinal cells (Osakada et al., 2009), functional liver tissue (Takebe et al., 2013), and dopaminergic neurons (Kriks et al., 2011). These strategies are approaching clinical testing, but the risk of iatrogenic malignancy remains a significant concern (Goldring et al., 2011; Lee et al., 2013). For example, cancers develop with increased frequency in induced pluripotent stem (iPS) cell-chimeric animals (Carey et al., 2010; Okita et al., 2007; Stadtfeld et al., 2010b), and neuronal tumors occur in primates injected with PSC-derived neurogenic cells (Doi et al., 2012). Most dramatically, an ataxia telangiectasia patient developed multifocal aggressive brain cancer following administration of neurogenic stem cells (Amariglio et al., 2009). These citations illustrate a need for effective and cancer-selective fail-safe mechanisms.

The causes of malignancy are not entirely clear. Reactivation of reprogramming factors, especially the *MYC* oncogene, has been implicated (Okita et al., 2007). However, cancers also occurred, albeit with lower frequency, when *MYC* was omitted form reprogramming protocols (Miura et al., 2009; Nakagawa et al., 2008; Werbowetski-Ogilvie et al., 2009). Notably, malignant and pluripotent cells show increased genomic instability, frequent and nonrandom chromosomal aberrations, and recurrent inactivation of canonical tumor-suppressor genes (Hussein et al., 2011; Marión et al., 2009; Mayshar et al., 2010). These findings suggest that initial barriers to transformation may be fortuitously inactivated in PSC and derived tissues.

Improved reprogramming procedures have greatly reduced, but not eliminated, the risk of cancer (Lee et al., 2013). These include nonintegrating and excisable vectors, the exclusion of *MYC*, and reprogramming by RNA, protein, or small molecules (Carey et al., 2010; Kaji et al., 2009; Stadtfeld et al., 2010a; Wernig et al., 2008). Additional strategies seek to purge residual PSCs, genomic surveys for somatic mutations, and conventional suicide genes (Choo et al., 2008; Tan et al., 2009). In this study, we explore a strategy based on recent insight into cancer's "oncogene dependence" (Jain et al., 2002; Soucek et al., 2008; Weinstein, 2002). We show that introduction of a dominant-negative *MYC* construct and temporary MYC inactivation can destroy aggressive iPS and embryonic stem (ES) cell-derived cancers while sparing healthy PSC-derived tissues.

RESULTS

To explore the MYC dependence of PSC-derived tissues, we introduced a dominant-negative MYC allele into karyotypically