Verma, 2014). Somatic cells likely mount barriers to reprogramming to avoid cellular transformation. Hence, it will be interesting to see whether newly identified roadblocks are also implicated in cancer development. At the moment it is unclear whether the small overlap of hits between the two studies is due to the species difference, the different markers used to isolate cell populations, or the studies not being comprehensive. In support of the latter explanation, it should be noted that several known reprogramming factors were not identified in the screens. For instance, in a similar approach Rais et al. found that Mbd3 RNAi together with OSKM transduction results in deterministic and synchronized iPSC reprogramming (Rais et al., 2013). However, Mbd3 was identified in neither the Qin et al. nor the Yang et al. studies. Therefore, extended RNAi screens will likely uncover even more genes that influence the efficiency and kinetics of iPSC generation. In any event, the presented data should broaden our understanding of the underlying mechanisms of reprograming. The challenging part will now be to combine reprogramming barriers whose combinatorial inhibition will have the largest impact on enhancing reprogramming efficacy and kinetics. In addition, it will be important to see whether the identified factors are fibroblast specific or if they are also roadblocks for reprogramming in other somatic cells. Recent studies have revealed contradicting results for factors implicated in reprogramming, where one group has found that Mbd3 depletion promotes reprogramming (Rais et al., 2013), whereas another group described that Mbd3 is required for efficient reprogramming (Dos Santos et al., 2014). There were a number of differences between the two experimental approaches that might account for this discrepancy. Nevertheless, this example illustrates the necessity to conduct detailed experiments under varying conditions to investigate the molecular mechanisms that operate during reprogramming. Therefore, the development of an optimized protocol demands a careful downstream analysis and a thorough investigation of the reprogrammed iPSCs, including the evaluation of their functionality as well as the verification of their genomic and epigenomic integrity (Liang and Zhang, 2013).

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Tipping the Balance: MTDH-SND1 Curbs Oncogene-Induced Apoptosis and Promotes Tumorigenesis

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Tumorigenesis is a complex and poorly understood process in which oncogenes can activate competing proapoptotic and proneoplastic programs. A recent paper in *Cancer Cell* demonstrates a dual role of the MTDH-SND1 complex in suppressing the apoptotic response and promoting breast cancer development, suggesting a new therapeutic avenue.

Tumorigenesis is a complex process in which cells typically acquire mutations that do not initially alter their biology, but ultimately lead to their transition into a state characterized by the possession of self-perpetuating, malignant properties. Several distinct molecular programs may contribute to this transition, but our knowledge of this aspect of oncogenesis is poor, particularly in epithelial carcinomas that are frequently not detected until after they are well established and often disseminated. Elucidating the relevant events that influence the speed and ability of individual cells to achieve this

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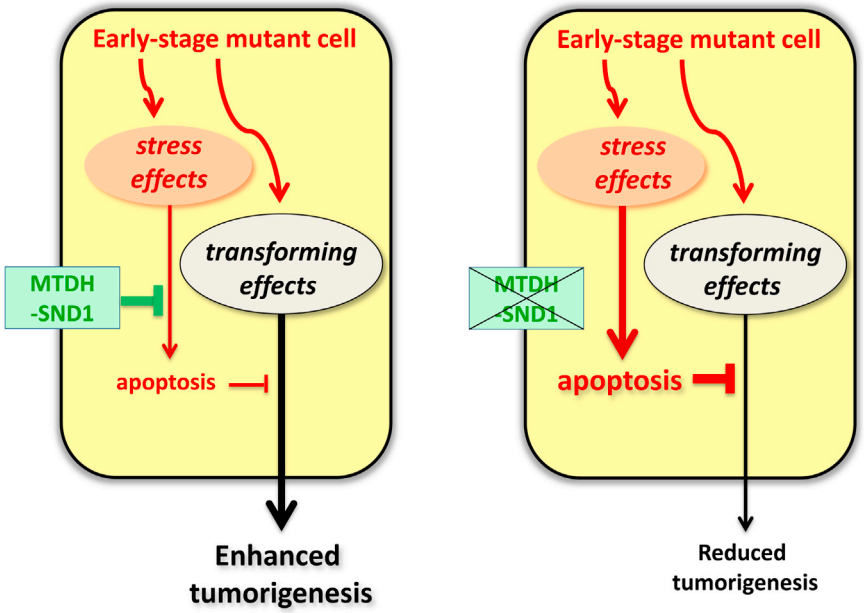

Figure 1. The MTDH-SND1 Prosurvival Complex Influences the Likelihood of the Creation of Tumorigenic Cells and the Maintenance of the Viability of Their Progeny

Oncogenic mutations in normal cells activate molecular programs involved in oncogenesis and the regulation of cell survival. The oncogenic stress response that activates the cell death machinery can be mitigated if the prosurvival MTDH-SND1 complex is intact (left cartoon). Disruption or blockade of the formation of this complex reduces the frequency of cells that acquire and maintain tumorigenic activity (right panel).

state is of major interest, because the knowledge gained may provide new clues for developing improved cancer therapies or even strategies for cancer prevention.

In the normal adult female mammary gland, two types of epithelial cells, an outer basal layer and an inner luminal layer of epithelial cells, must execute a combination of survival, proliferation, self-renewal, and differentiation programs to meet changing physiological demands. In humans (Kannan et al., 2013, 2014) and likely in mice (Artandi et al., 2000; Diehn et al., 2009), this results in the creation in situ of cells that are highly prone to mutagenesis, potentially increasing their probability of subsequent malignant transformation. Recently in *Cancer Cell*, Kang and colleagues describe a new mechanism that antagonizes both the oncogene-activated and DNA-damage-enhanced sensitivities to apoptosis that are already apparent in the preneoplastic cells generated in multiple models of breast cancer induction. Interestingly, disrupting this mechanism was also found to determine the probability and pace of subsequent tumor formation (Wan et al., 2014).

Metadherin (*MTDH*; also known as *Astrocyte elevated gene 1* (*AEG1*)) is a little-studied gene located on human chromosome 8q22, a region that is frequently amplified in many cancers including those arising in the breast. Kang and colleagues now demonstrate that loss of MTDH delays the appearance of tumors in four different mouse models of breast cancer (three different oncogene- and one carcinogen-induced model) consistent with a documented reduction in the frequency of cells with operationally defined, transplantable "tumor-initiating cell" (TIC) activity. More detailed analyses showed that loss of MTDH also increased the frequency of apoptotic cells selectively among either basal or luminal mammary cells, depending on which subset was undergoing oncogene-activated hyperplastic transformation. Because the authors had previously shown that MTDH forms a stable intracellular complex with Staphylococcal nuclease domain-containing 1 (SND1), itself a known prosurvival factor (Blanco et al., 2011), their next step was to use a vector-mediated shRNA knockdown approach to examine the potential role of SND1 in mediating the same effects caused by loss of MTDH. What they found was that, in the same breast cancer induction models, loss of either component of the complex phenocopies loss of the other (Figure 1). Through additional experiments that identified a specific SND1-binding motif in MTDH, Wan et al. (2014) were also able to show that disruption of the interaction between these two proteins was sufficient to erode the prosurvival roles of either one in oncogene-stressed mammary epithelial cells.

The authors also created an *Mtdh*-knockout-*LacZ*-knockin mouse. Examination of the females revealed MTDH to be a ubiquitously expressed protein but one, nevertheless, that is not required for normal mouse development or fertility, nor for the formation of a normal mammary gland. Using an assay in which the mammary stem cells are enumerated based on their ability to regenerate a complete new gland when transplanted at limiting dilutions into the mammary fat pad of new female host mice, Wan et al. (2014) further showed that neither the production nor the regenerative activity of this primitive subset of normal mammary cells is dependent on the MTDH-SND1 complex.

Together these findings suggest that MTDH is not essential for the homeostatic control or functionality of any normal mammary epithelial cell type, either basal or luminal. On the other hand, in both of these cell types, the MTDH-SND1 complex plays an important role in reducing the proapoptotic effect of oncogene activation, even before the cells begin to display fully malignant properties.

Importantly, Wan et al. (2014) also provide persuasive evidence that these findings are relevant to human breast cancer. They first demonstrate that reducing MTDH or SND1 activity in either transformed human breast cancer cell lines or patient-derived xenografts decreases the frequency of cells that initiate tumor formation in vivo (in xenografted, immunodeficient mice). In addition, analysis of human breast cancer microarray data sets revealed strongly correlated expression of these two proteins in individual patients' tumors and an inverse correlation between their expression and the response of the tumor to standard therapy. These findings suggest that expression of these markers is indicative of a bad prognosis in human breast cancer.

The molecular mechanisms through which the MTDH-SND1 complex protects cells against oncogenic stress will be very interesting to investigate in the future. Amplified *MTDH* has also been reported to enhance breast cancer tumor cell metastasis, raising the question of how this is achieved. Since SND1 has been shown to be a component of the multiprotein RNA-induced silencing complex (RISC), where it has a stabilizing function (Tsuchiya et al., 2007), it may be interesting to explore the possibility that the MTDH-SND1 complex could influence microRNA expression.

An important aspect of the study by Wan et al. (2014) is their finding that MTDH is expressed in many tissues. This suggests that the role of the MTDH-SND1 complex in breast cancer formation may be shared by tumors in other tissues, such as the liver and colon (Huang et al., 2014; Yoo et al., 2009). In addition, the results of Wan et al. (2014) illustrate how important, and potentially clinically exploitable, insights can be gained from analyzing early events in tumorigenesis, here exemplified by the identification of a cell-intrinsic mechanism that appears to promote oncogene/carcinogen-induced tumorigenesis by reducing a coinduced proapoptotic response. Antiapoptotic mechanisms are well-known to play a key role in the creation of a malignant state; for example, via mutations in *BCL2*, *TP53*, and *MYC* (Cotter, 2009). However, these latter examples have usually been associated with the blockade of an apoptotic mechanism that normally serves to control mature cell numbers in the tissue. In contrast, the antiapoptotic mechanism of interest here appears to act indirectly by enhancing the probability that a cell will survive deleterious effects of genomic perturbation. The evidence suggesting that increased expression of the MTDH-SND1 complex in human breast cancer is an indicator of poor prognosis suggests the possibility of targeting this complex for therapeutic intervention, and the identified interaction site between MTDH and SND1 provides a potential starting point for such an endeavor.

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