The transcription factor Oct4 plays a central role in controlling the undifferentiated state of embryonic and induced pluripotent stem cells. Two complementary papers in this issue of Cell Stem Cell describe the extended network of proteins that interact with Oct4. Together, these studies broaden our understanding of the control of pluripotency.

The protein Oct4 (also known as Pou5f1) lies at the heart of the transcriptional regulatory network that is responsible for establishing and maintaining the pluripotent state in embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) (Nichols et al., 1998; Takahashi and Yamanaka, 2006). Numerous studies have shown that the trio of Oct4, Sox2, and Nanog cooccupy large ensembles of target genes resulting in both positive and negative regulation (Chambers and Tomlison, 2009). Moreover, the transcriptional regulation of these three factors relies on a recursively wired circuit with auto and cross-regulatory loops. Oct4 is also critical in reprogramming somatic cells to a pluripotent state (Takahashi and Yamanaka, 2006; Hochedlinger and Plath, 2009). The levels of Oct4 must be tightly controlled, as indicated by the fact that 2-fold alterations result in dramatic changes in stem cell fate. Despite the wealth of available information, extended Oct4 protein-protein interaction networks have not been defined. Previous studies have begun to identify proteins that interact with Oct4 and Nanog, although these were limited to small sets of interacting partners (Wang et al., 2006). Two papers in this issue, by van den Berg et al. (2010) and Pardo et al. (2010), make substantial progress in describing detailed Oct4-centered interactome networks in mouse ESCs. Together they provide a “snapshot roadmap” that gives us insights into how this key transcriptional regulator functions and how its activity may be integrated with other cellular processes.

Both studies relied on improved affinity “tagging” methodologies to obtain much more extensive interactomes than previous analyses. A number of identified interactions are consistent between the two data sets, which increases overall confidence in the biological significance of the results, but detailed comparisons have not yet been made (Figure 1). There are also, however, significant and noteworthy differences. For example, in the van den Berg et al. paper, Oct4 is shown to interact with the transcription factor Esrrb, although this factor does not meet the criteria to be included in the interactome presented by Pardo et al. This is an important discrepancy that needs to be resolved, given the important role that Esrrb plays in pluripotency and its known interactions with Nanog (Wang et al., 2006). In addition, van den Berg et al. make the interesting observation that Esrrb interacts with the basal transcriptional machinery. Pardo et al., on the other hand, include Nanog in the Oct4 interactome, whereas van den Berg et al. do not. The basis of this discrepancy also needs to be clarified. There are also other differences, and at this point it is not clear whether a single combined Oct4-centered interactome would be more accurate if constructed as a union or intersection of the two data sets.

Despite the differences between these two studies, there is a high degree of consistency and numerous common “motifs” emerge. For example, interactions with chromatin-modifying complexes such as NuRD and SWI/SNF appear in both interactomes. One recent study has shown that SWI/SNF is required for ESC differentiation (Schaniel et al., 2009). In general, the issue of how various epigenetic modifying complexes interact with the transcriptional regulatory machinery is of great importance. Both van den Berg et al. and Pardo et al. found that the expression level of a large proportion of interacting proteins is controlled by Oct4 and other stem cell transcription factors. This observation underscores the intricate linkages between transcriptional regulatory networks and protein-protein interaction networks. In addition, many components in the Oct4 interactomes are downregulated upon differentiation. The overall architectures of the two interactomes also display common features such as the presence of network hubs with a high degree of interconnectivity. A very important set of insights from the two papers is how the pluripotency network, which is largely specific to stem cells, is integrated with more “generic” components of cells. For example, there are connections with well-known components of cell signaling and DNA repair pathways. Clearly, changes in cell fate must take place within the context of the machinery that is responsible for such general features of cells. It will be interesting to see how other cell type-specific interactome networks interface with this general machinery. Particularly interesting will be to ask how interactomes centered on proteins shared by closely related cell populations are similar as well as different. Good candidate cell populations for such comparisons could be different types of related stem cells, for example, ESCs, trophectoderm stem cells, and extraembryonic endoderm stem cells.

The two studies therefore provide a solid foundation for further analyses. However, a number of issues still need to be addressed. These include the apparent discrepancies between the identified interactomes highlighted above. In addition, because of experimental limitations, these kinds of studies necessarily represent “average” interactomes. There
is no guarantee that the extensive protein-protein interaction networks described exist in entirety in individual cells. Extending network analyses to individual cells is currently not possible; however, one could envisage monitoring limited protein-protein interactions in single ESCs by using fluorescence resonance energy transfer or related techniques. In addition, these network ensembles must by their very nature be dynamic, but presently we are limited to providing network “snapshots.” Methodologies need to be developed to measure network dynamics in real time and as a function of transitions in cell fate. One recent paper describes the beginnings of such analyses after shRNA-mediated down-regulation of Nanog (Lu et al., 2009). This paper also highlights the necessity of integrating dynamic data sets obtained at multiple molecular and biochemical levels. For example, to gain a complete picture of how pluripotency is regulated, it will be important to analyze changes in epigenetic modification, active transcription, mRNA levels, protein levels, etc., all in the context of evolving changes in cell fate. At this point, van den Berg et al. and Pardo et al. provide much “food for thought” and a valuable framework for future efforts to understand how cell fate regulatory information “flows” and is processed to bring about an observable change in cellular phenotype.

**REFERENCES**


**Figure 1. Overlap between Oct4 Interactomes**

A comparison of the Oct4 interactomes identified in the van den Berg et al. and Pardo et al. papers. Note that the intersection includes 20 proteins. This degree of shared proteins will require further clarification.

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**The Hair Follicle Bulge Stem Cell Niche Resists Transformation by the Hedgehog Pathway**

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Similarities between basal cell carcinoma (BCC) tumor cells and hair follicle keratinocytes had previously suggested that BCC originates within the hair follicle bulge stem cell niche. However, in the current *Nature Cell Biology, Youssef et al. (2010)* show that BCC instead originates in the interfollicular epidermis.

Tumors have been commonly classified based on their similarity to the normal tissues from which they are derived, both at the level of architectural features and protein expression. Within normal somatic tissues, there is significant heterogeneity among cell subpopulations with regard to their proliferative capacity, differentiation, and susceptibility to malignant transformation. Given the dynamic changes that occur during tumorigenesis, determining the specific cell of origin for any