Retinoic acid and BMP4 cooperate with p63 to alter chromatin dynamics during surface epithelial commitment.

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Public Summary:
A developing embryo faces the difficult task of concocting myriad tissue types — including skin, bone and the specialized glop that makes up our internal organs and immune system — from essentially the same set of ingredients: immature, seemingly directionless stem cells. Although some of the important players that provide direction to this transformation are known, it's not been clear exactly how they work together to accomplish this feat. Now, researchers at the Stanford University School of Medicine have identified a key regulatory hierarchy in which proteins called morphogens control gene expression by directing the looping of DNA in a cell. This looping brings master regulators called transcription factors in contact with specific sets of genes necessary to make particular tissue types.

Scientific Abstract:
Human embryonic stem cell (hESC) differentiation promises advances in regenerative medicine(1-3), yet conversion of hESCs into transplantable cells or tissues remains poorly understood. Using our keratinocyte differentiation system, we employ a multi-dimensional genomics approach to interrogate the contributions of inductive morphogens retinoic acid and bone morphogenetic protein 4 (BMP4) and the epidermal master regulator p63 (encoded by TP63)(4,5) during surface ectoderm commitment. In contrast to other master regulators(6-9), p63 effects major transcriptional changes only after morphogens alter chromatin accessibility, establishing an epigenetic landscape for p63 to modify. p63 distally closes chromatin accessibility and promotes accumulation of H3K27me3 (trimethylated histone H3 lysine 27). Cohesin HiChIP(10) visualizations of chromosome conformation show that p63 and the morphogens contribute to dynamic long-range chromatin interactions, as illustrated by TFAP2C regulation(11). Our study demonstrates the unexpected dependency of p63 on morphogenetic signaling and provides novel insights into how a master regulator can specify diverse transcriptional programs based on the chromatin landscape induced by exposure to specific morphogens.