

Developmental Cell
Article

CellPress

A LncRNA-MAF:MAFB Transcription Factor Network Regulates Epidermal Differentiation

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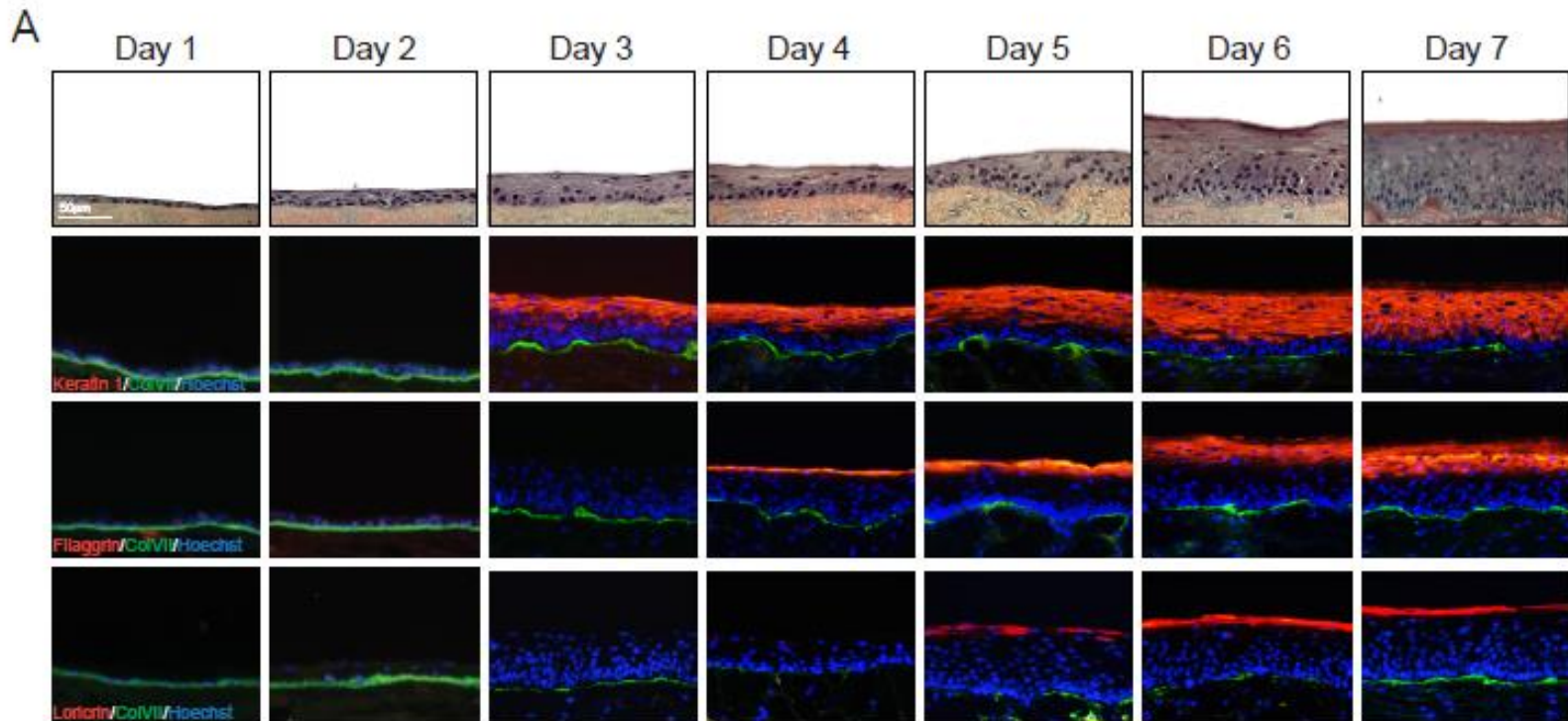
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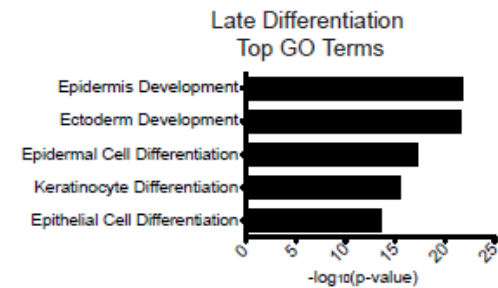
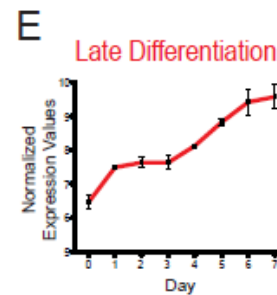
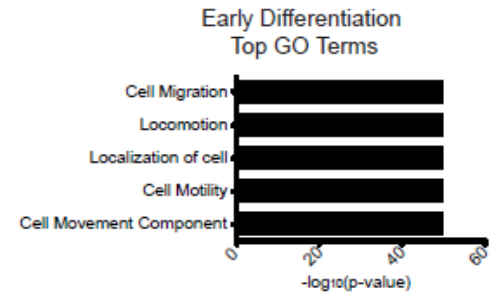
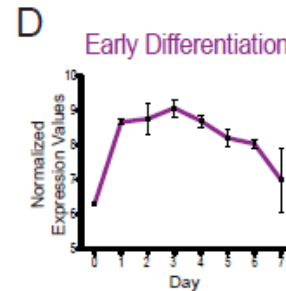
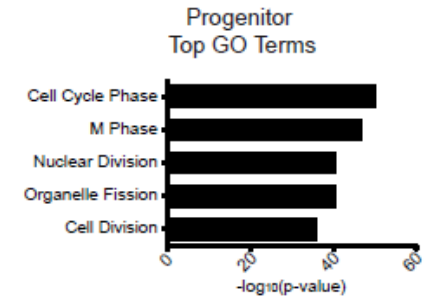
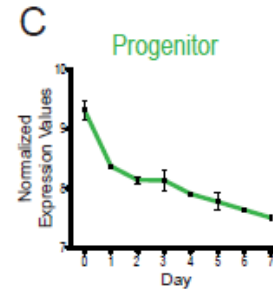
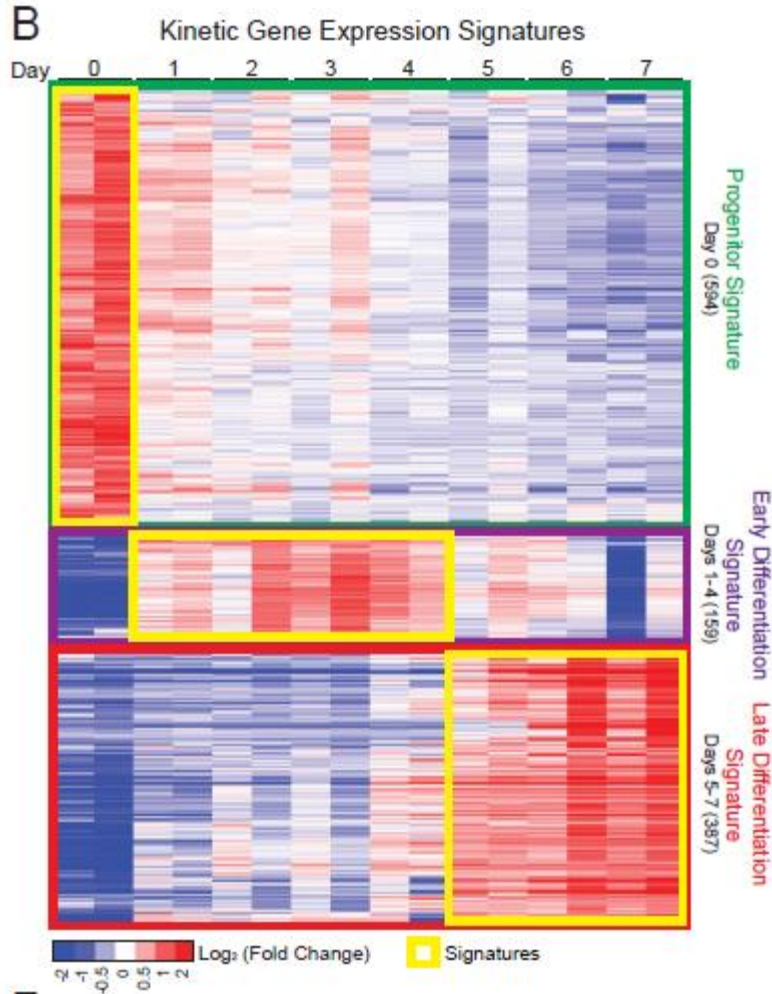
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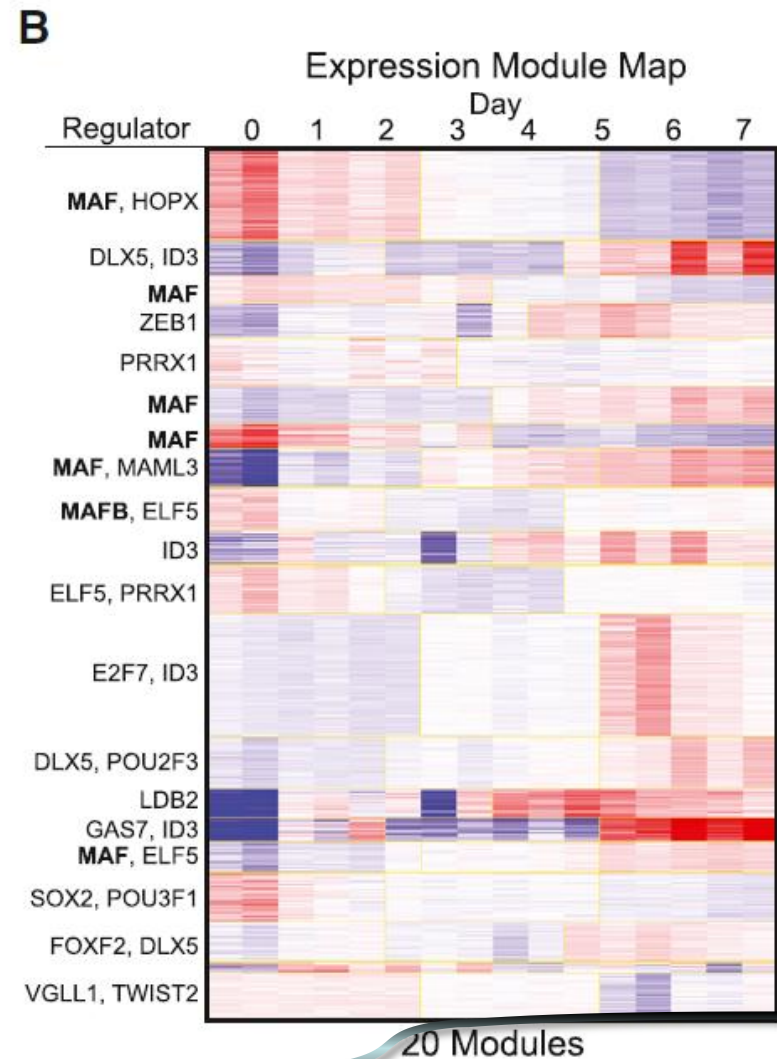
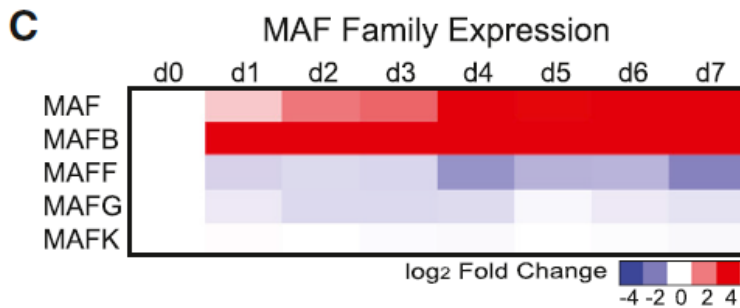
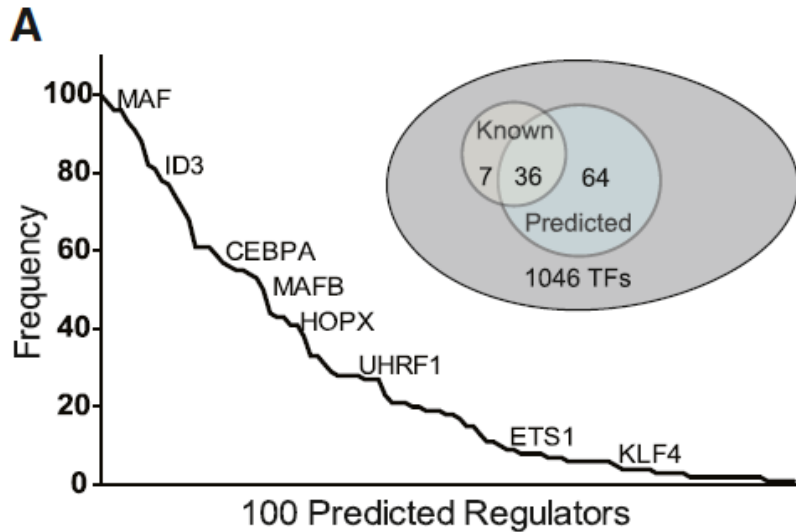
<http://dx.doi.org/10.1016/j.devcel.2015.01.028>

Kinetic transcriptome analysis during regeneration of differentiated epidermal tissue

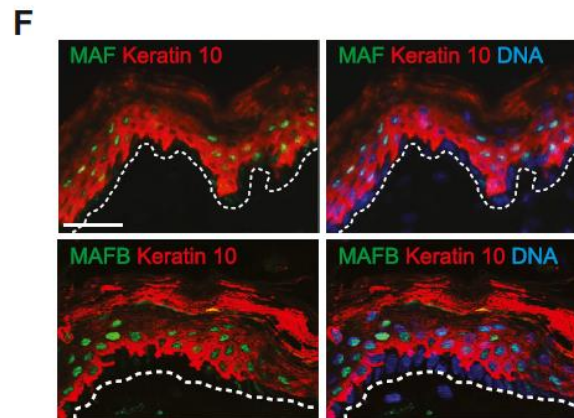
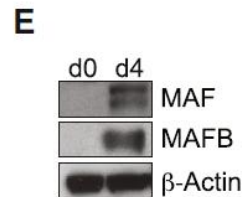
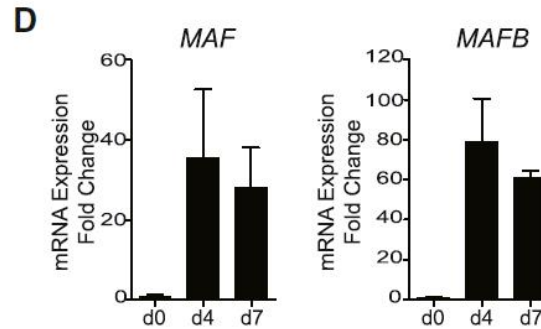


Kinetic transcriptome analysis during regeneration of differentiated epidermal tissue





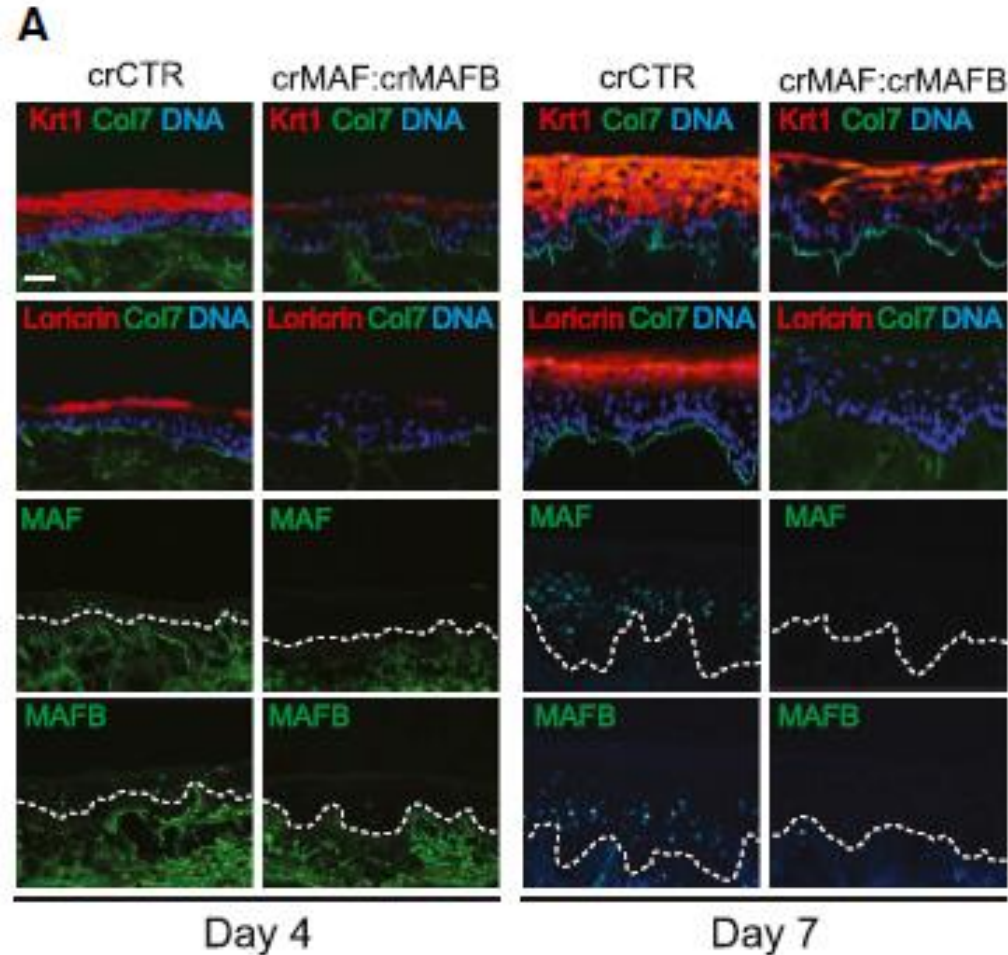
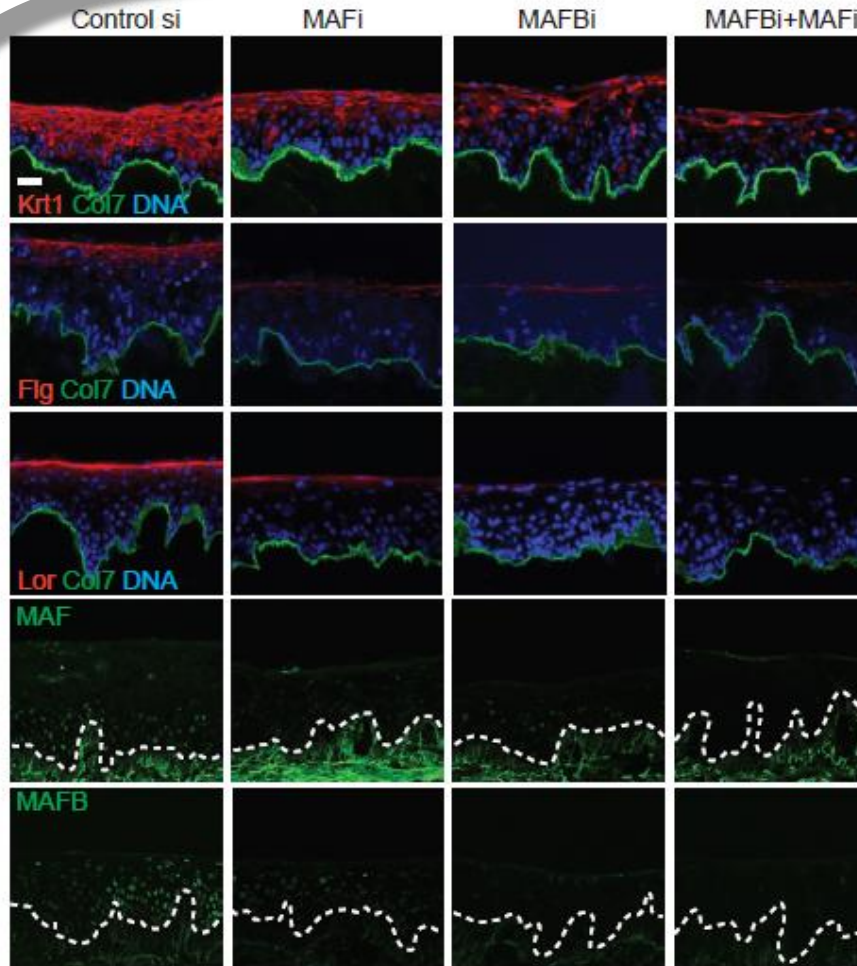
Module mapping identifies MAF and MAFB on epidermal differentiation



Normal Human Skin

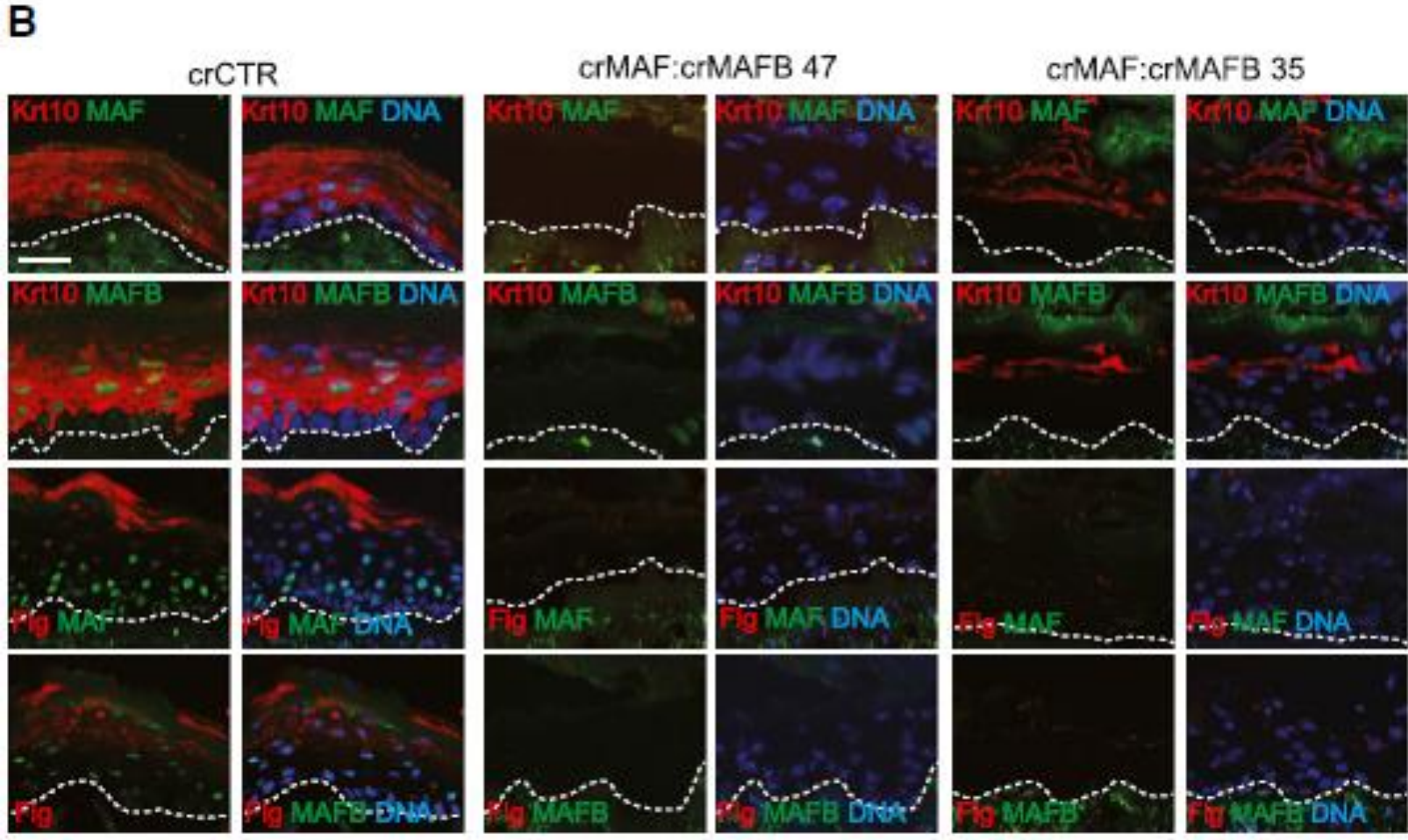
MAF:MAFB in the differentiated suprabasal layers of the epidermis

MAF:MAFB is necessary and sufficient to drive epidermal progenitor differentiation



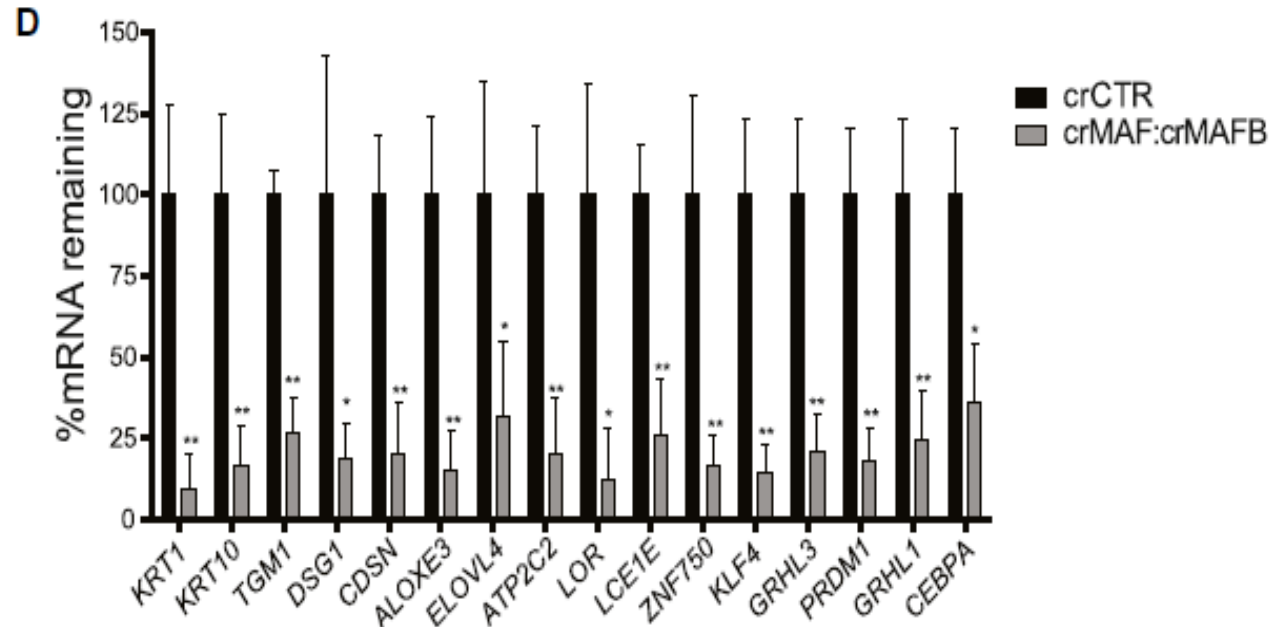
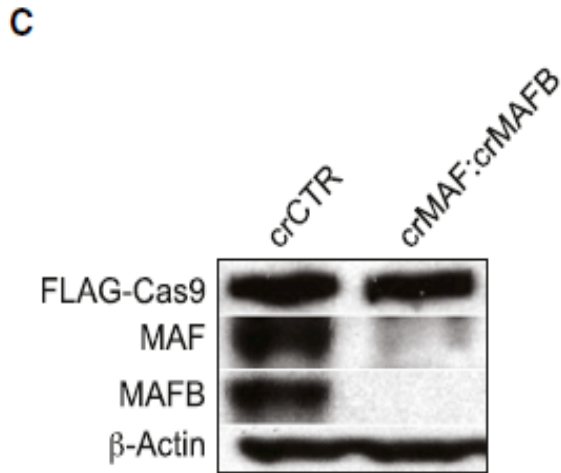
Indicates that MAF:MAFB is essential for differentiation gene induction, but not stratification.

MAF:MAFB is necessary and sufficient to drive epidermal progenitor differentiation



Day 21 (*In vivo*)

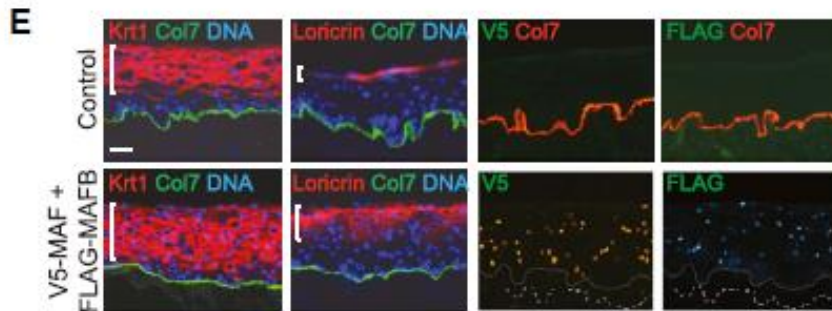
MAF:MAFB is necessary and sufficient to drive epidermal progenitor differentiation



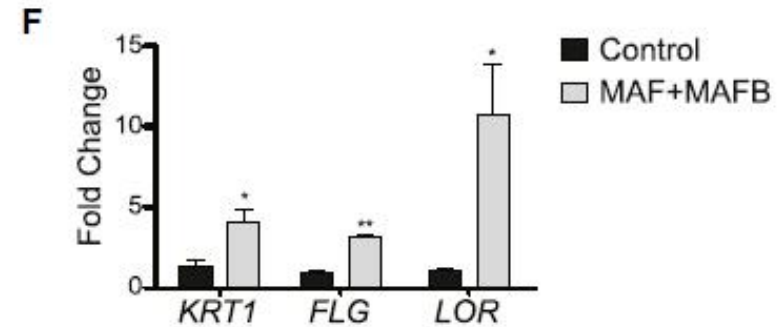
- Mitotic index increased (Ki67 staining)
- Decreased apoptotic index (TUNEL staining)

These results, along with prolonged differentiation gene expression defects, suggests an important role for MAF:MAFB in the maintenance of epidermal homeostasis.

Can enforced expression of MAF:MAFB in progenitor populations drive epidermal differentiation?

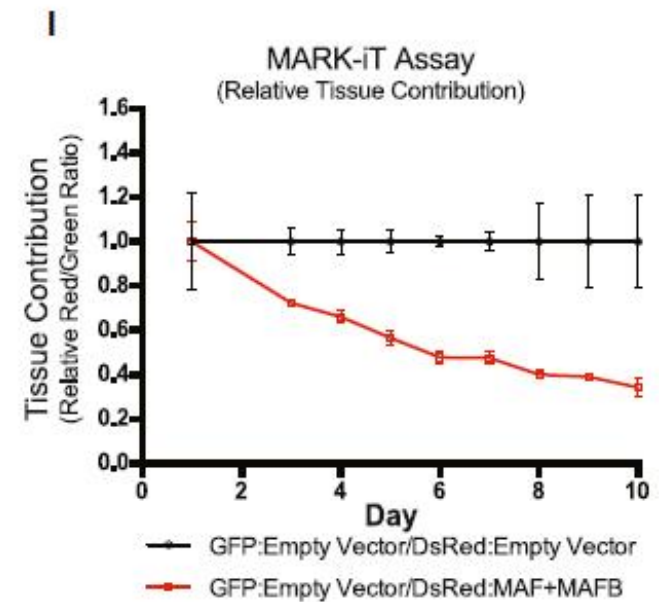
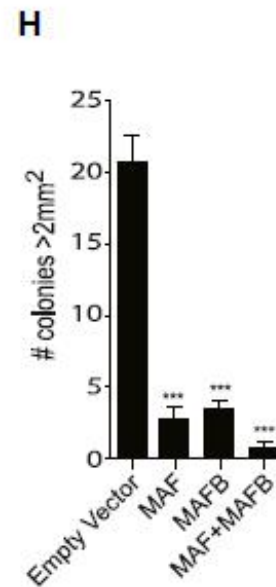
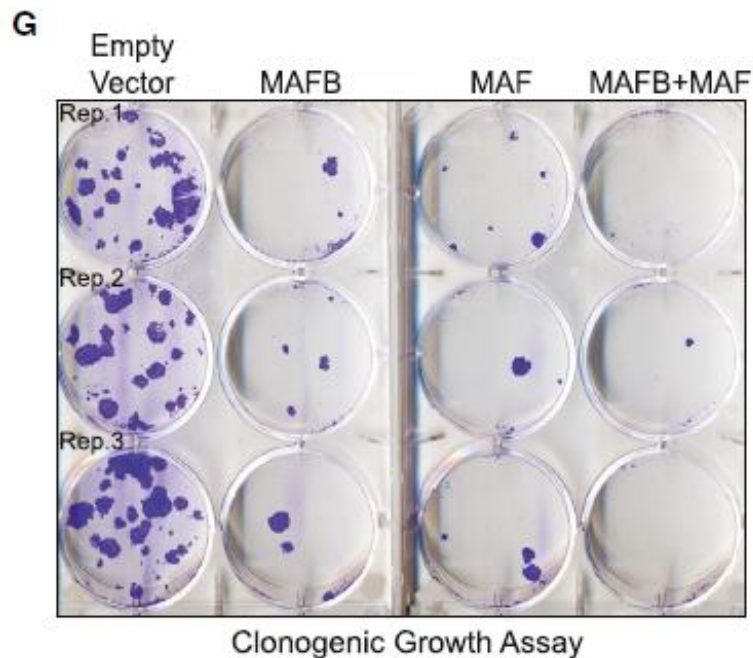


Aberrant basal and spinous layer expression

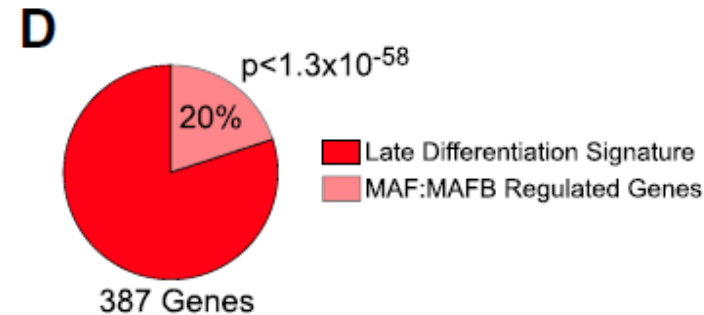
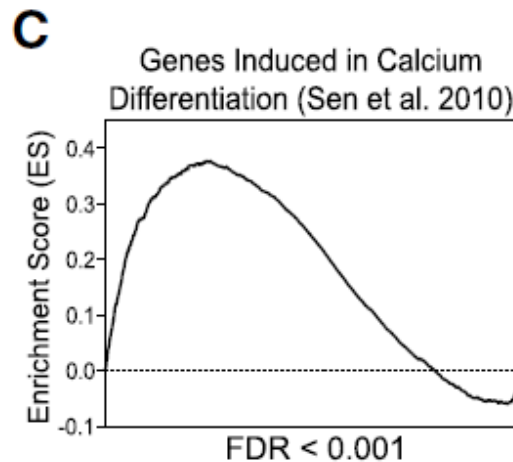
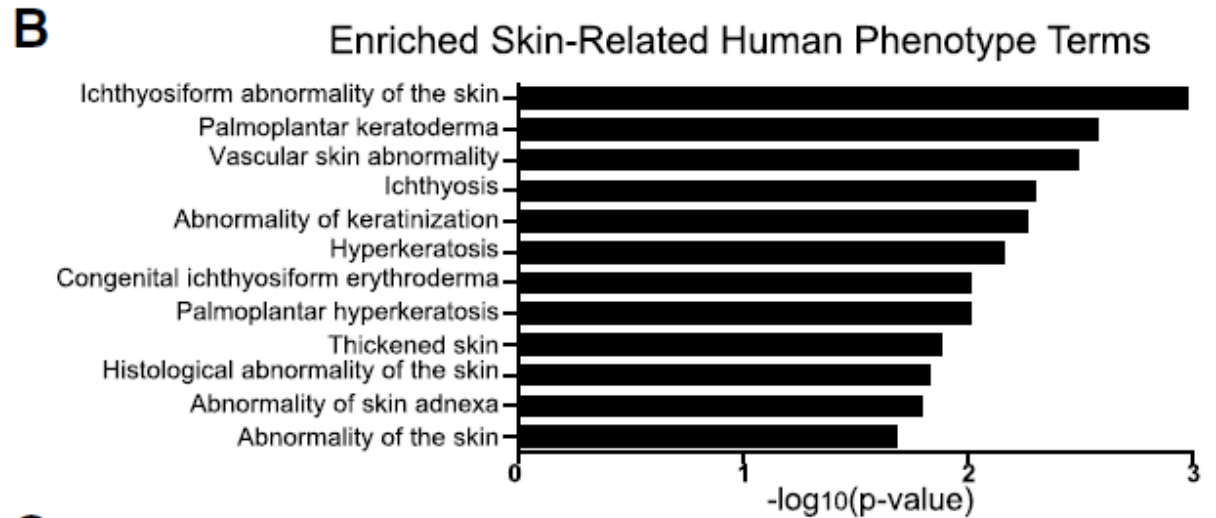
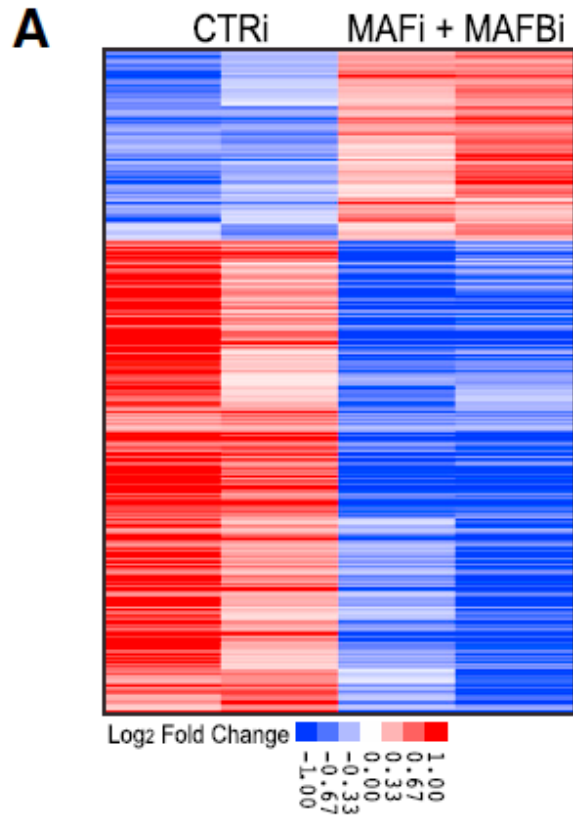


This supports the sufficiency to drive ectopic differentiation in less differentiated epidermal cells.

Does MAF:MAFB suppress epidermal progenitor self-renewal?



In addition to being essential of differentiation, MAF and MAFB oppose proliferative self-renewal, consistent with their role in epidermal differentiation.

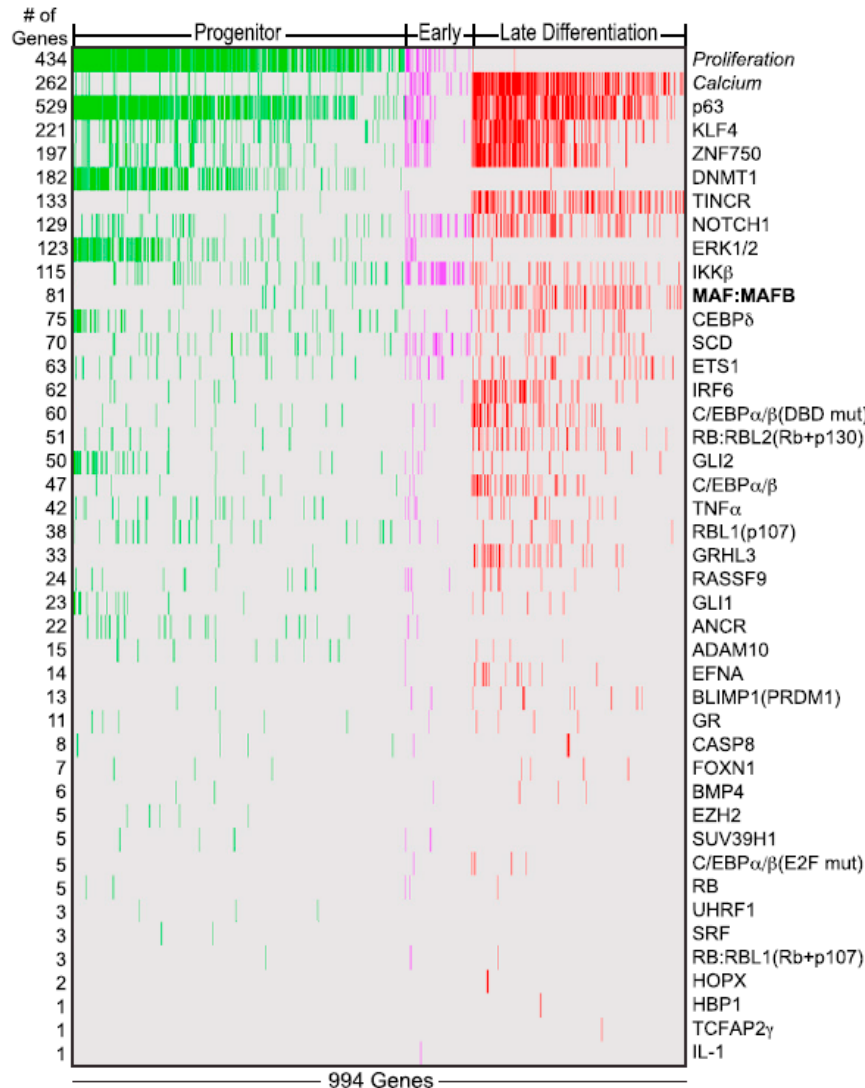


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MAF:MAFB is required for induction of a substantial portion of the differentiation gene set.

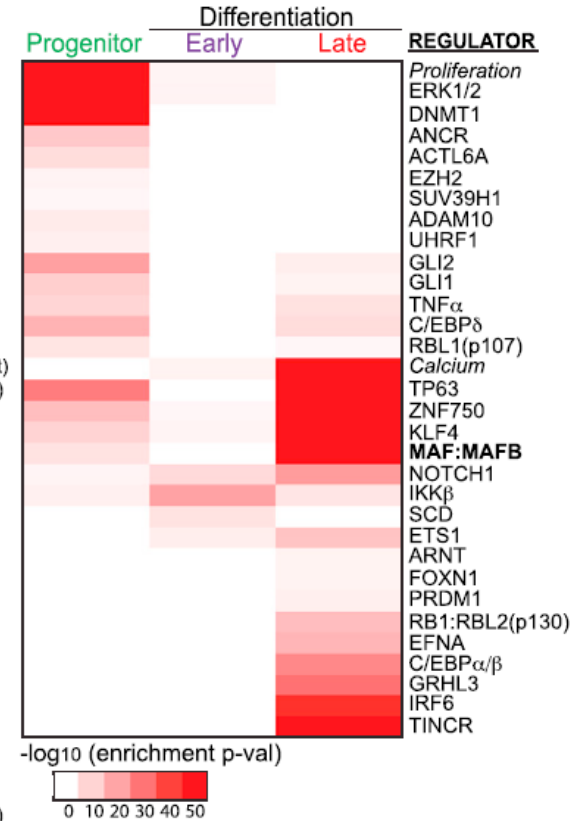
Comparison to other epidermal regulators

Catalog of Differentially Expressed Genes in Epidermis

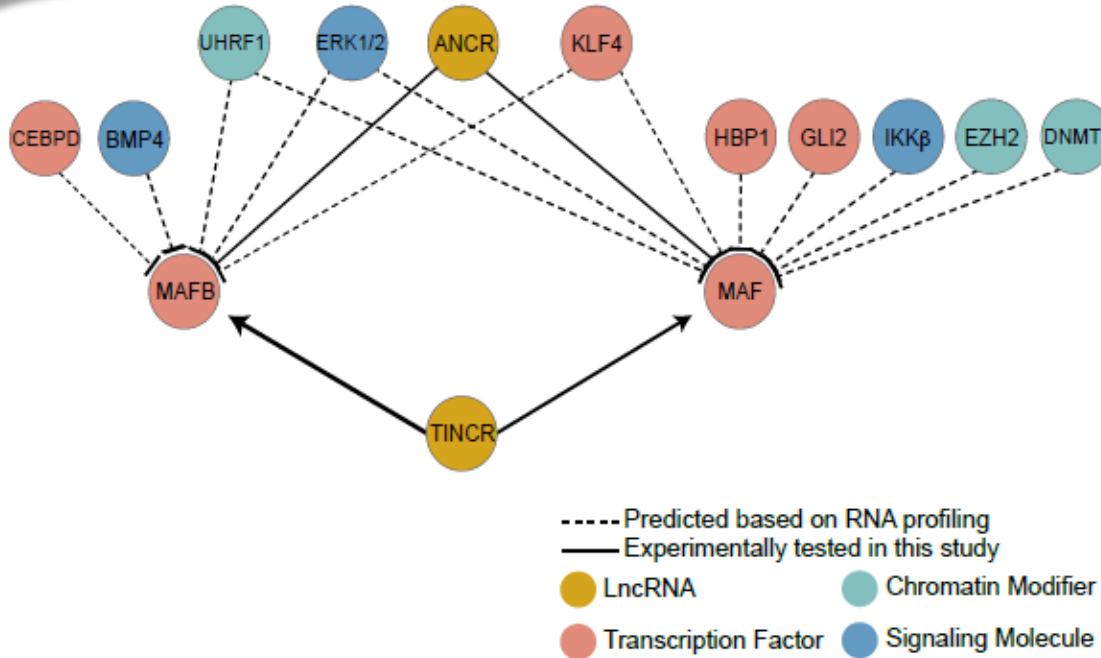


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Multi-Dimensional Gene Set Enrichment Analysis



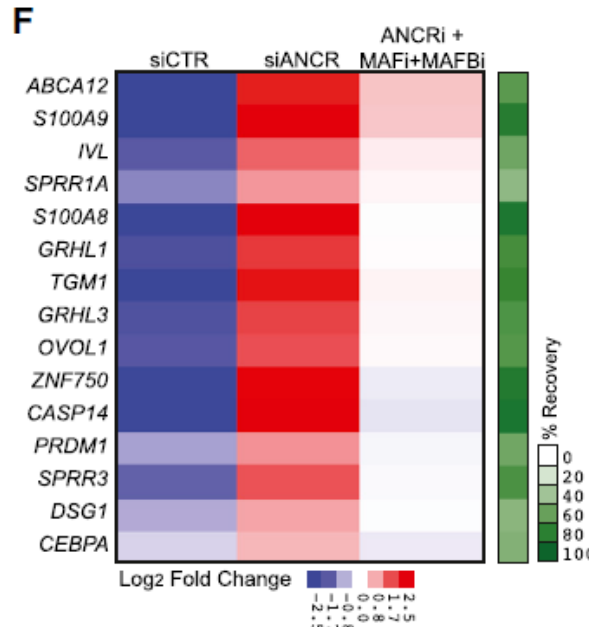
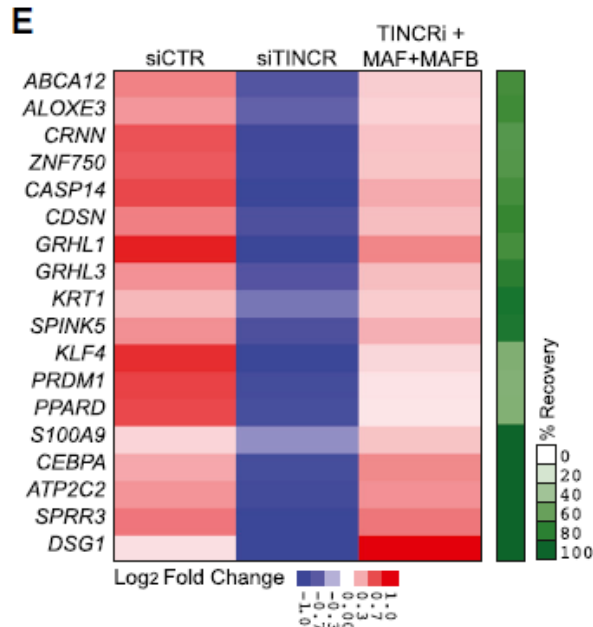
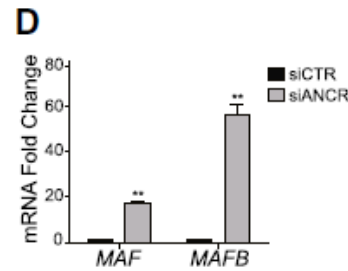
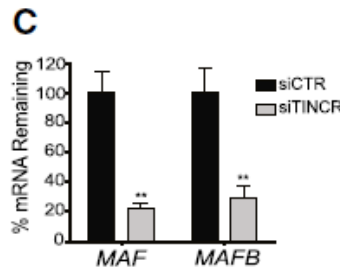
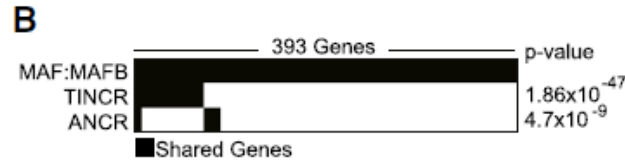
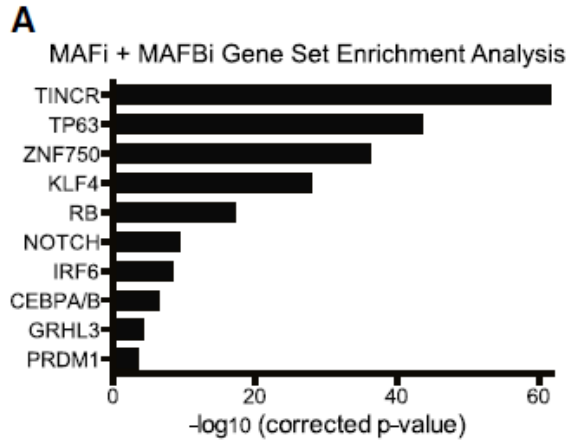
LncRNAs are upstream regulators of MAF-MAFB



ANCR: the anti-differentiation lncRNA, promotes progenitor maintenance and recently has been shown to prevent differentiation in osteoblasts by interacting with EZH2 to suppress gene activation. ANCR, was predicted to act as an MAF:MAFB **repressor**.

TINCR: the terminal differentiation-induced lncRNA, promotes terminal differentiation through a mechanism involving direct RNA:RNA interactions and recruitment of STAU1 protein to stabilize differentiation-specific mRNAs. TINCR, was predicted to act as an MAF:MAFB **activator**.

LncRNAs are upstream regulators of MAF-MAFB

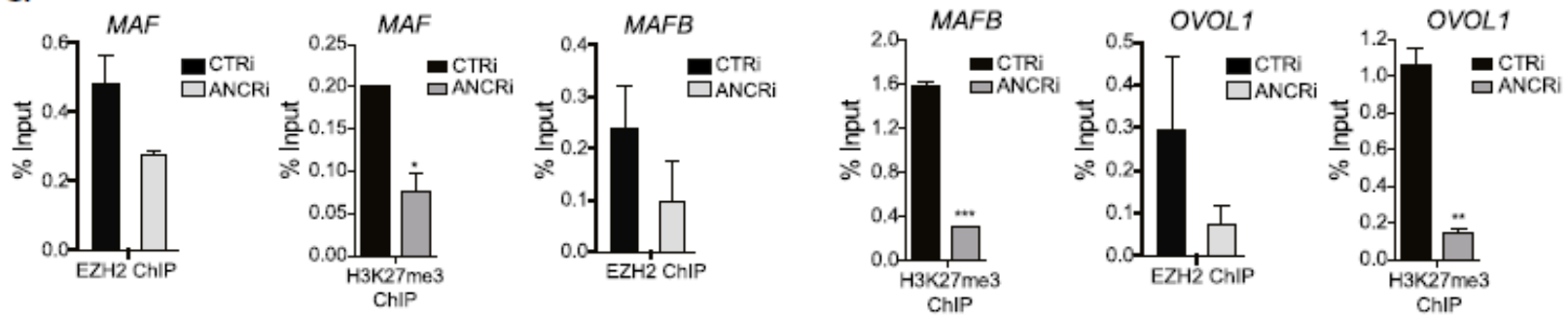


MAF:MAFB can partially rescue the differentiation defects produced by TINCR loss.

Partial reduction in diff. gene induction was observed – ANCR progenitor maintenance is sustained by the repression of MAF:MAFB

LncRNAs are upstream regulators of MAF-MAFB

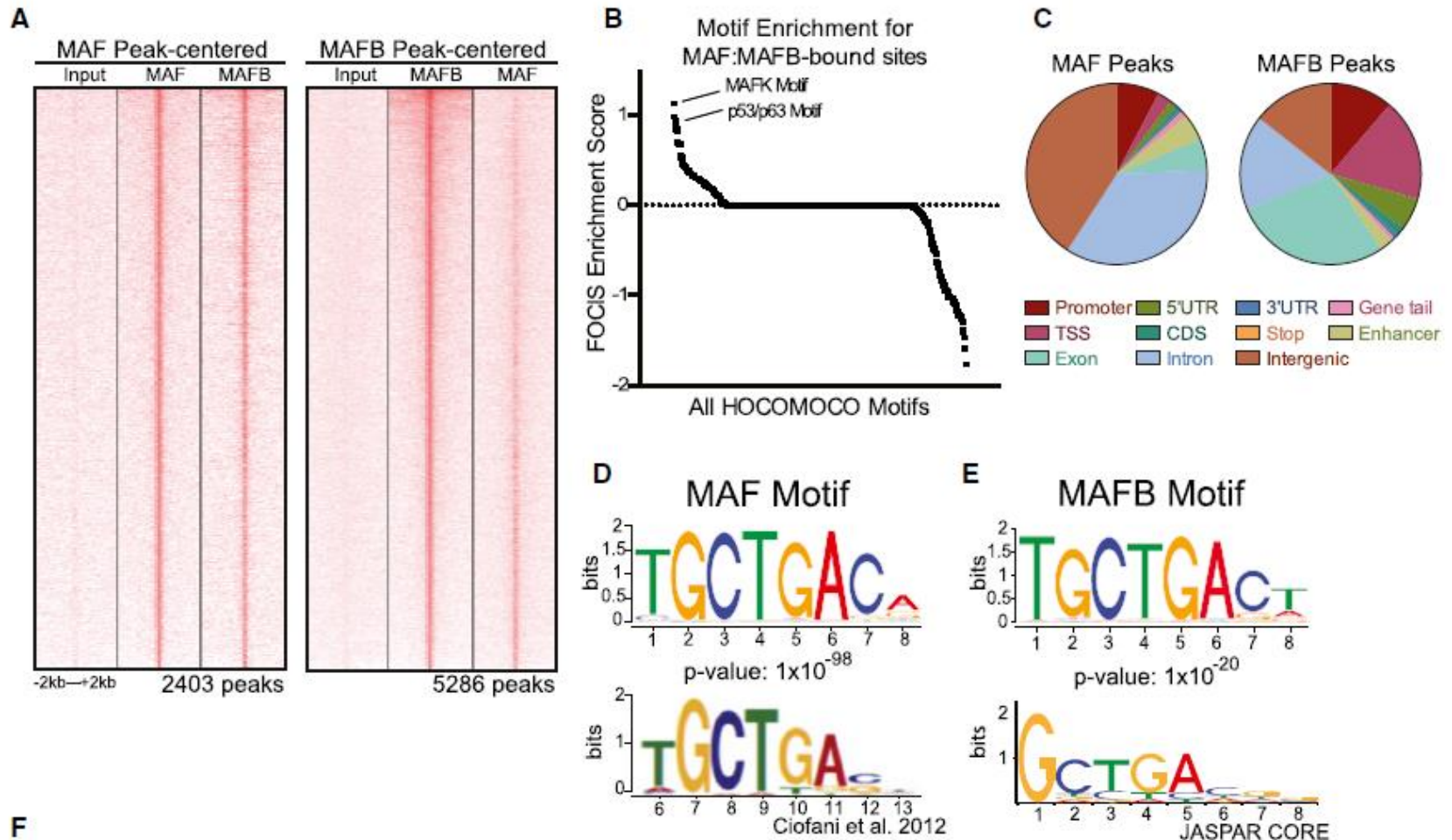
(CHIP)-qPCR of EZH2 and H3K27me³ - assess EZH2 recruitment to ANCR-repressed diff. genes.



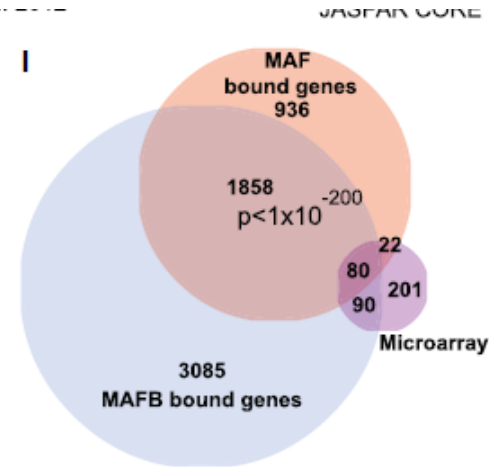
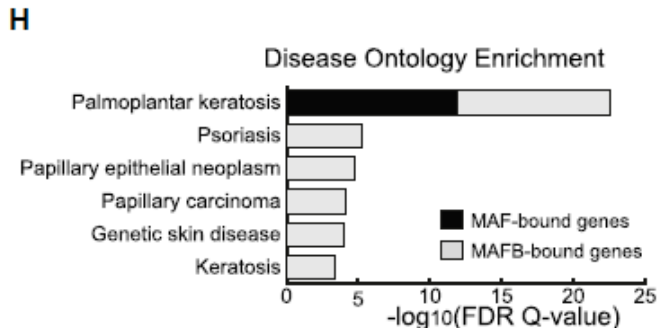
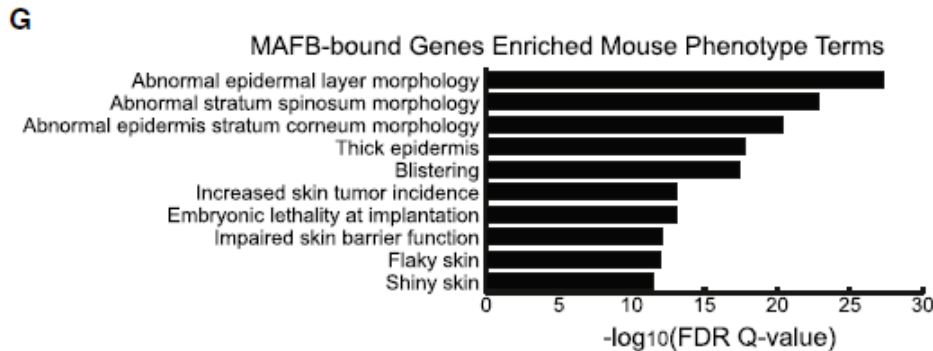
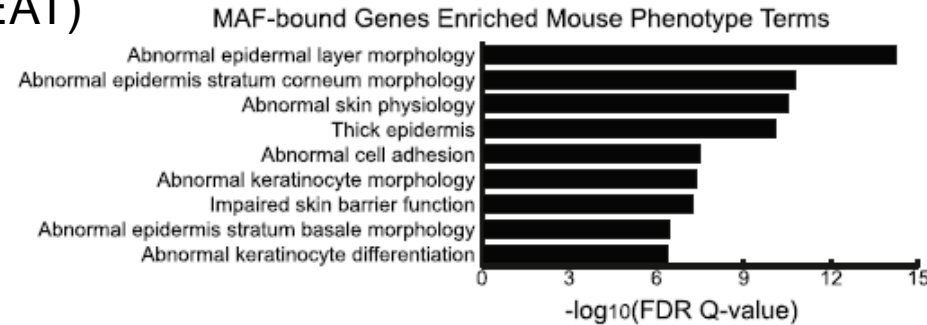
Taken together these results point to ANCR and TINCR lncRNAs as upstream regulators of MAF:MAFB, whereby ANCR represses MAF:MAFB in association with EZH2 gene targeting to prevent premature MAF:MAFB-driven progenitor differentiation, and whereby TINCR potentiates differentiation gene expression through enhancement of MAF:MAFB mRNA stability.

Genome-wide MAF:MAFB occupancy in differentiation

Which are direct downstream effectors of MAF:MAFB-driven differentiation?



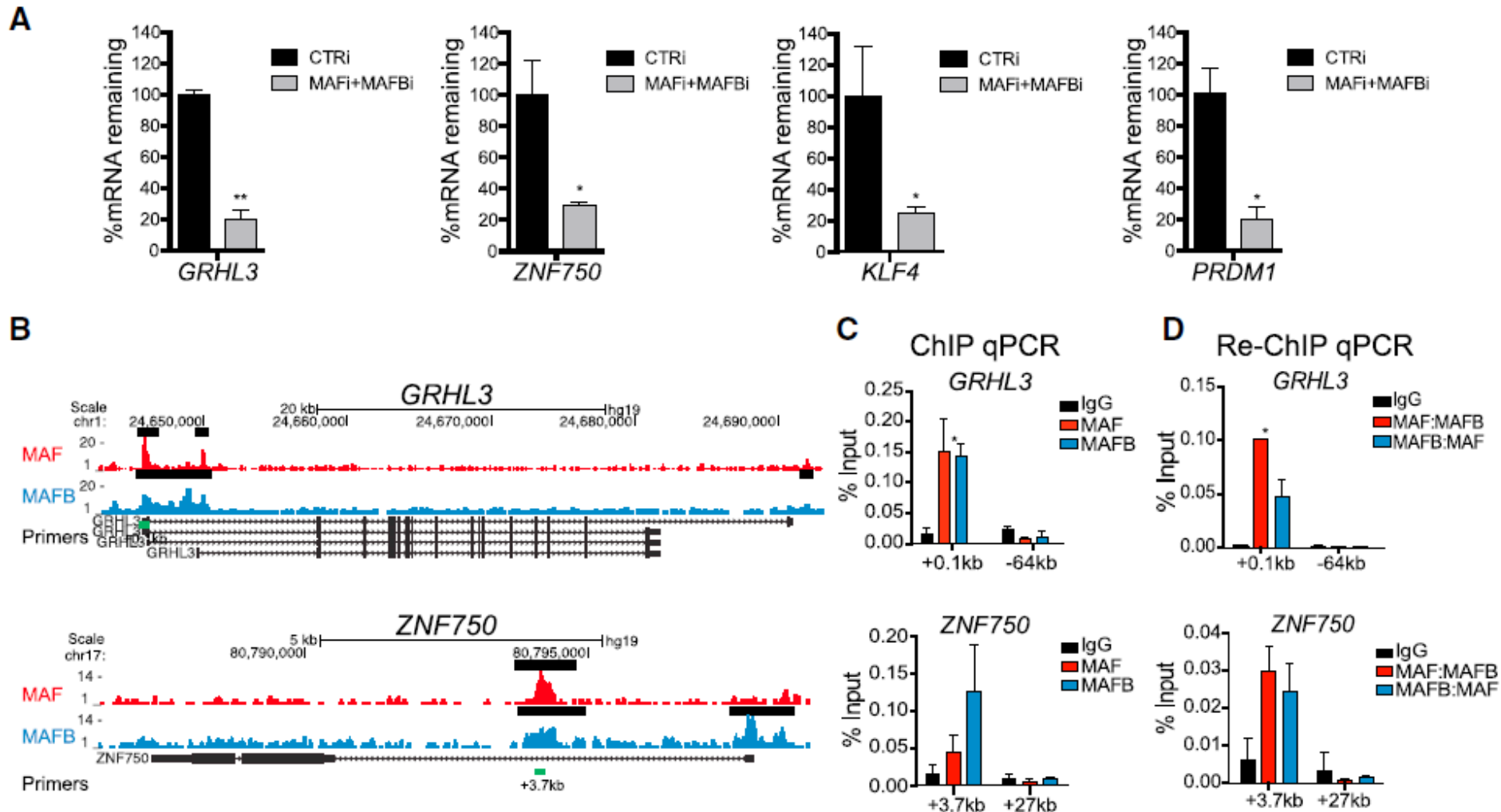
Genomic Regions Enrichment of Annotations Tool (GREAT)



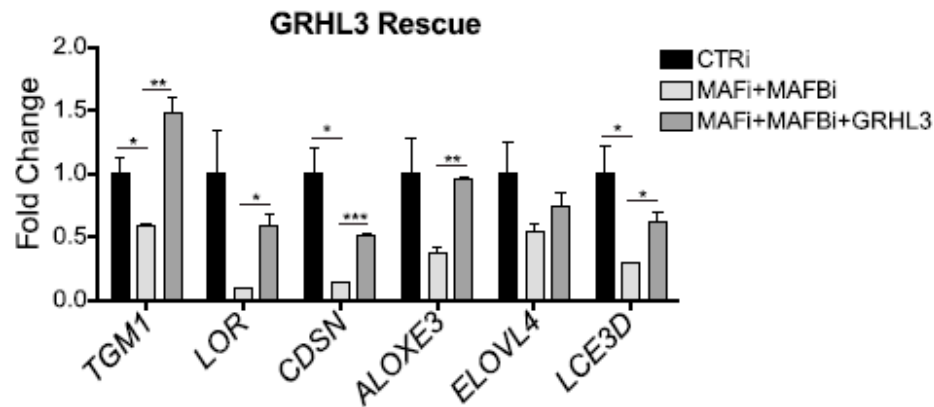
J MAF:MAFB Bound and Regulated Genes

ABHD10	DUSP1	LRMP	RIT1
ABHD5	DUSP14	MAF	RORA
AGA	EGLN3	MAFB	RPS6KA5
AHNAK	ETS2	MAG1	SEMA6D
ANAPC1	FNIP2	MAP3K1	SERPINB8
ARFGEF1	FOSL2	MAP3K8	SLC22A23
ATP11B	FOXN3	MED13L	SNX9
AVP1	GRHL1	MGST3	SRGAP2
BNIP3L	GRHL3	MYO6	TACC2
C10orf99	HECA	NDFIP2	THRB
CAPNS2	HOOK1	NFE2L3	TNFRSF11A
CD36	IMPA2	NHP2L1	TNFSF10
CDS1	IPPK	NXN	TRAP1
CSNK1A1	KAT2B	PDLIM1	TUBB
CSRP2	KCNK1	PFN2	UBE2J1
CXADR	KLF4	PRDM1	UBL3
CYP2J2	KRT78	PRRG4	YPEL2
DDX3X	KRT80	PTPN1	ZBTB43
DHX40	LPIN1	PTPN3	ZCCHC6
DNAJB6	LPP	RBMS1	ZNF750

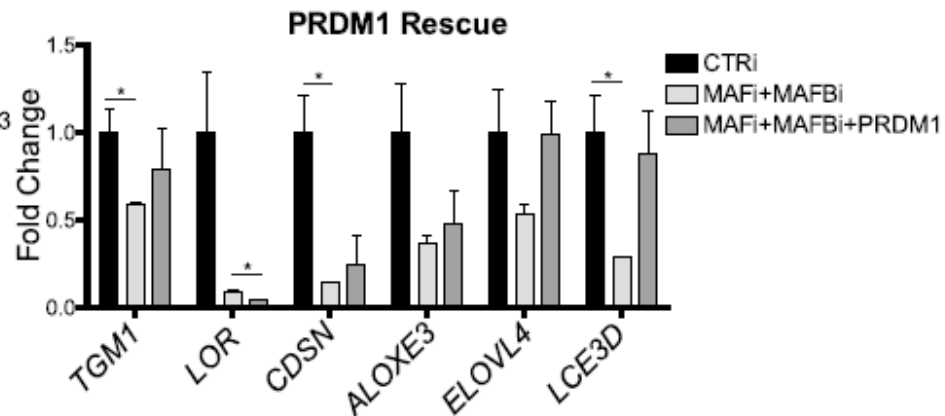
MAF:MAFB regulates epidermal TFs



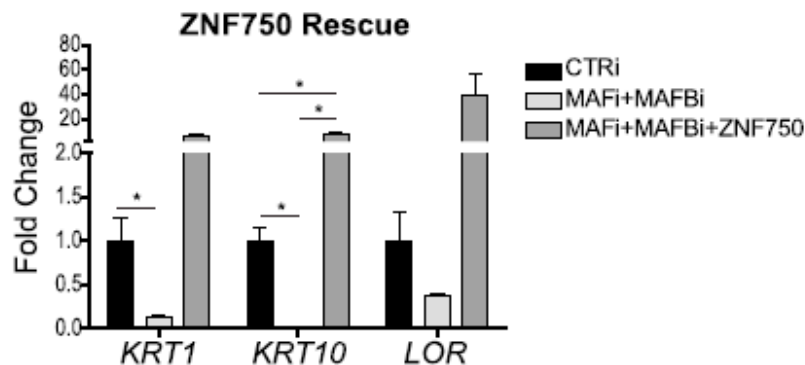
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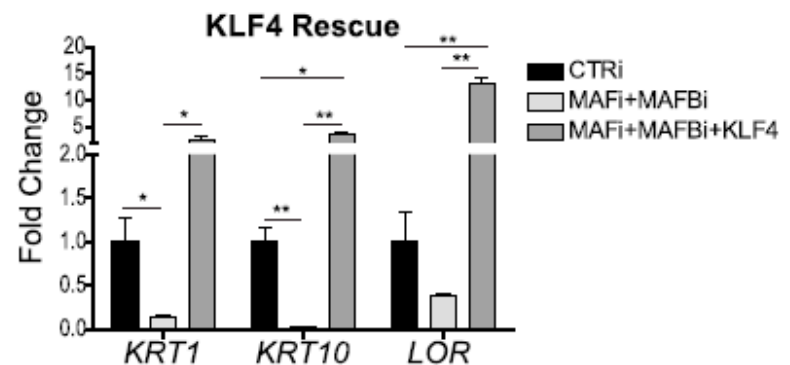
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These findings suggest that MAF:MAFB controls the expression of epidermal differentiation-inducing TFs that, in turn, act downstream of MAF:MAFB to activate discrete gene subsets in the epidermal differentiation program.

Summary

