Chromatin modfiers in endometrial cancer

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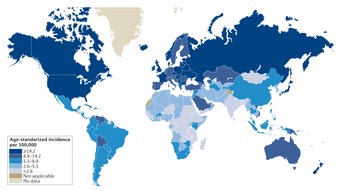
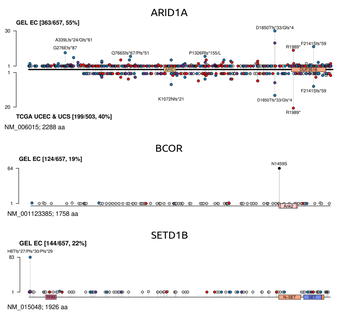
Endometrial cancer - most frequent gynecological



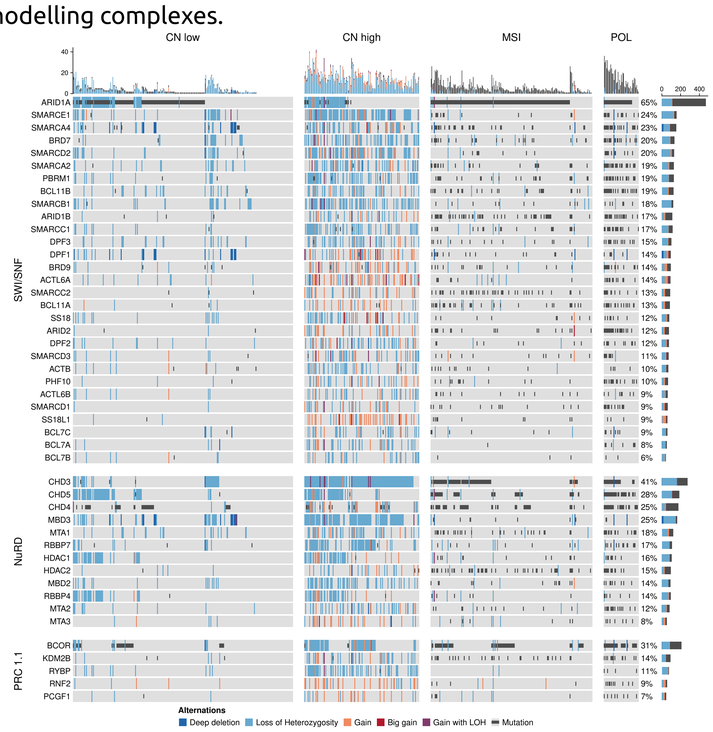
Endometrial cancer (EC) - cancer of the lining of the uterus, is the most common gynecological cancer in the UK and US. In 2020, there were **417,000 new diagnoses**. EC is the 6th leading cause of cancer-related deaths among women in the US and 8th in Europe.

Chromatin modifiers are frequently altered in EC

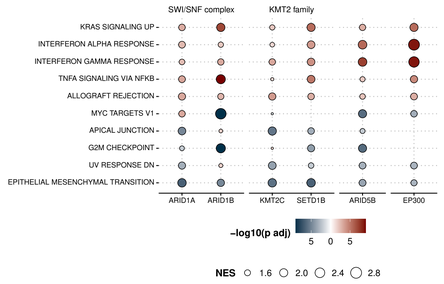
Mutations are often found in chromatin modifiers. ***ARID1A*** is characeterized by truncating mutations. ***BCOR*** **N1459S** hotspot mutation is near unique to EC. Frameshifts are also frequent in other chromatin modifiers such as ***ARID5B*** or ***SETD1B***.



Alterations in chromatin modifiers differ with respect to EC molecular subtype. Modifications are found in various members of chromatin remodelling complexes.



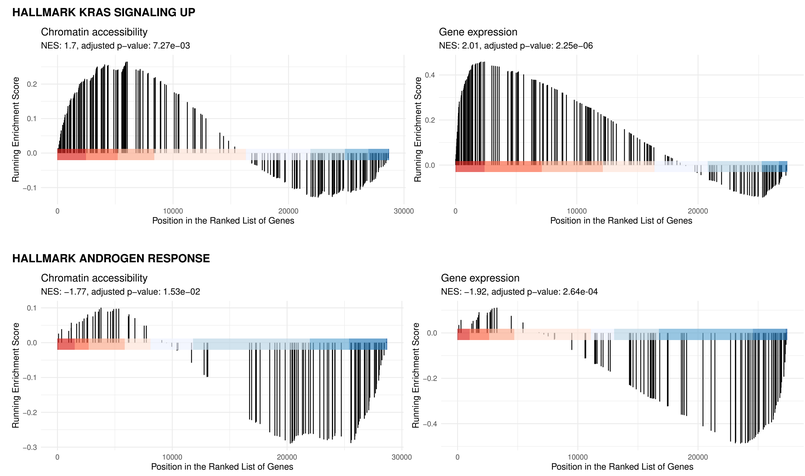
Loss of chromatin modifiers changes chromatin organization and transcriptome profiles



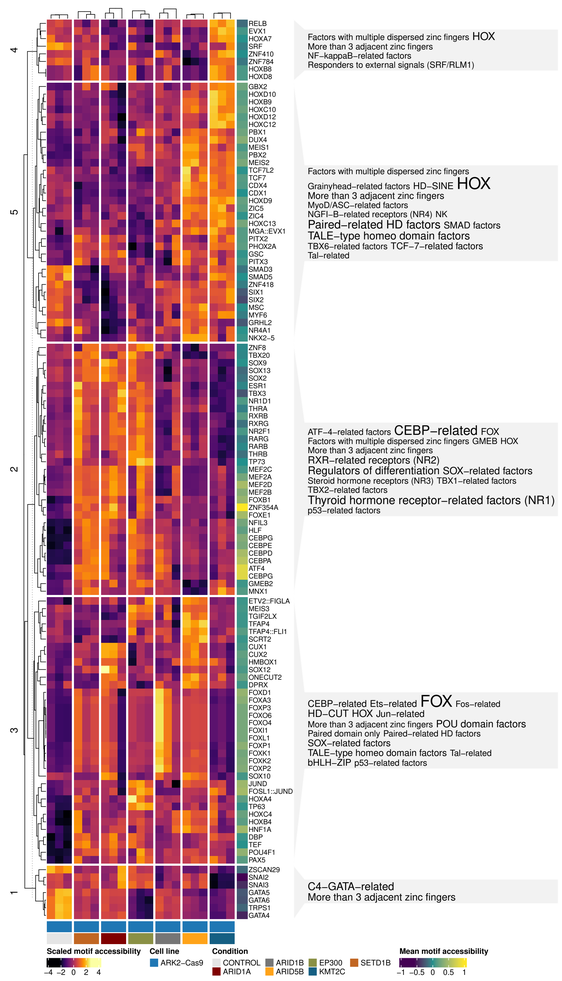
Loss of chromatin modifiers up-regulates **KRAS signaling pathway** and interferon responses.

EMT is down-regulated at the gene set level, however several genes such as ***SPOCK1*** or ***IGFBP2*** are up-regulated.

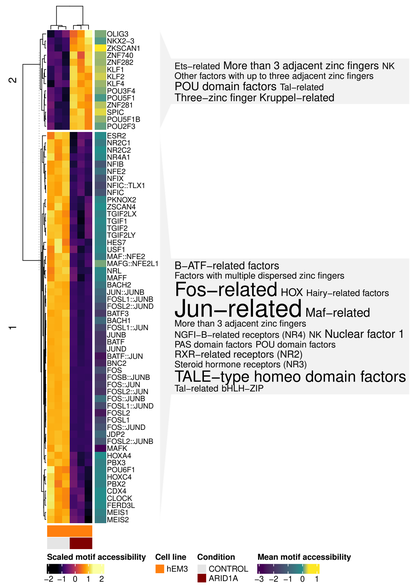
Dysregulation of pathways is driven by the altered chromatin accessibility. Up-regulation of **KRAS signaling** in Ark2 Cas9 *SETD1B* knock-out and down-regulation of **Androgen response** in Ark2 Cas9 *KMT2C knock-out* shown below.



Loss of chromatin modifiers results in changes in transcription factors motifs accessibility

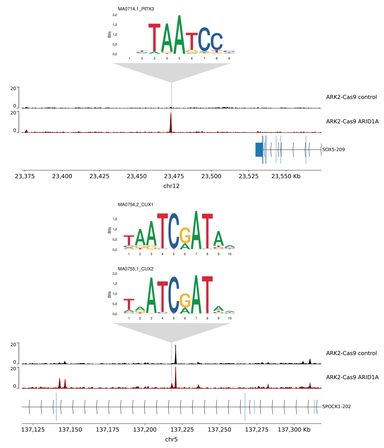


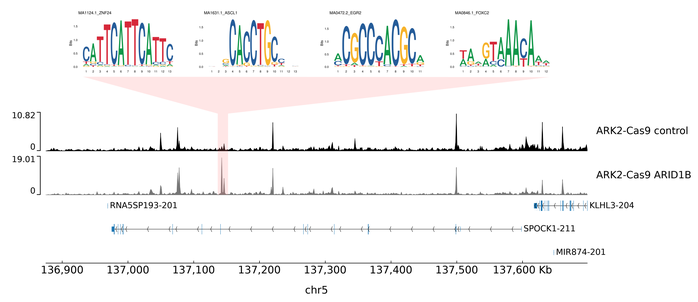
Loss of SWI/SNF components results in changes in the accessibility of TF motifs



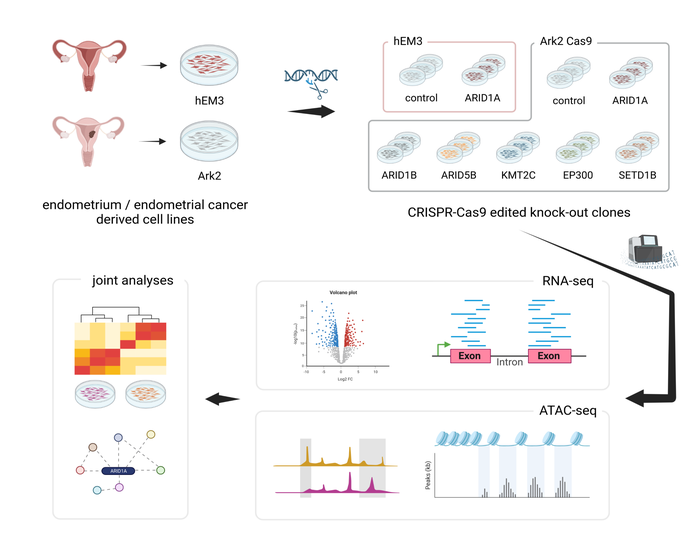
Loss of ARID1A in normal endometrium cell line model results in increased accessibility of **Kruppel-related** (such as KLF1, KLF2 and KLF4) and **Three-zinc finger** (ZNFs) transcription factors. 30% of Cluster 2 motifs are found within 3,000 bp of TSS, while more than 44% of KLF motifs are located in promoter regions.
At the same time, accessibility at the motifs of **Jun-related** and **Fos-related** TFs is reduced. 21% of Cluster 1 motifs are found in promoter regions while 29% are found in intergenic regions. Only 18% of Fos and Jun-related motifs are found within 3,000 bp from TSS.

Loss of ARID1A in EC cell line model results in increased accessibility of **CUX1**, **CUX2** and **PITX3** motifs. Those motifs are found in accessible sites around important genes, such as ***SOX5*** - TF involved in differentiation and linked with ERK pathway or ***SPOCK1*** - member of the EMT pathway (shown on the right). Loss of ARID1B in EC cell line model results in appearance of accessibility site at intronic region of ***SPOCK1*** gene with a cluster of TF motifs (below).





Methods overview



Conclusions

For the first time, **we describe the gene expression and chromatin accessibility profiles as an effect of chromatin modifiers loss**. The investigation of chromatin modifier knockouts revealed dysregulation of critical pathways such as **KRAS signaling**, **TNF-α/NF-κB signaling**, **interferon responses**, and the down-regulation of **EMT**. Loss of chromatin modifiers, often observed among EC patients, **results in changes in chromatin accessibility and accessibility of TF motifs**.

Our findings underscore the consequences that loss of chromatin modifiers has to the chromatin accessibility and gene expression profiles, as well as the potential compensatory mechanisms cancer cells employ in response to the loss of chromatin modifiers.

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