Chromatin Organization Analysis of EGFR in Various Human Cancer Samples

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Introduction

- The epidermal growth factor receptor (*EGFR*) gene and its related pathway is aberrant in various human cancers.
- *EGFR* pathway analysis is currently limited to the genome and transcriptome.
- Structural variants (SVs) are large scale alterations in chromosome or DNA structure.
- Hi-C contact maps provide novel structural variant analysis of the chromatin in cancer cells.
- Chromatin interaction around EGFR may reveal unique insight into non-coding regions involved in the *EGFR* pathway.

Methods

- Alteration and mRNA expression analysis of *EGFR* using the NCI60 cell line library (accessed from cBioPortal[1].
- Juicebox[2], a Hi-C visualization tool, was used to depict chromatin interaction.
- SV-induced chromatin interactions were identified by Neoloopfinder[3].
- The chromatin organization of a non-cancerous cell line (HUVEC) was compared to five cancer tissue samples (glioblastoma multiforme, leiomyosarcoma, esophageal adenocarcinoma, chondrosarcoma, and chordoma).

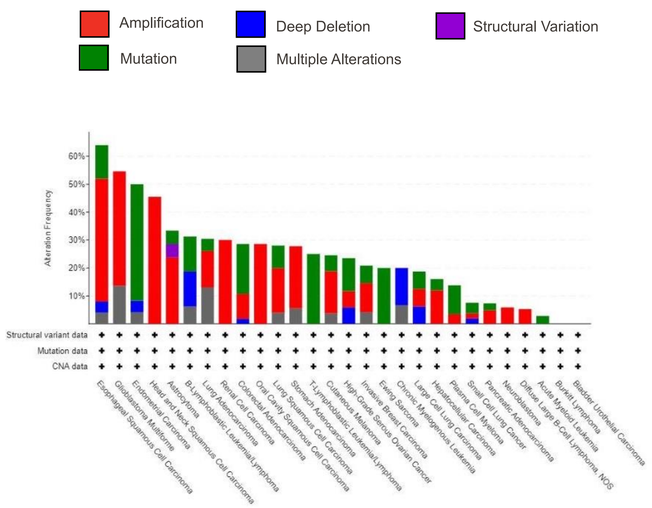

Fig.1 *EGFR* alteration analysis

cBioPortal revealed that various *EGFR* alterations are exhibited across human cancers.

Results

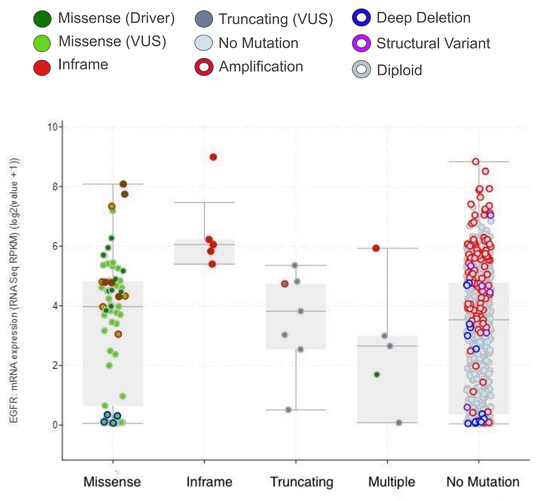

Fig.2 mRNA expression analysis of *EGFR*

cBioPortal revealed increased mRNA expression with structural variant associated alterations and amplifications.

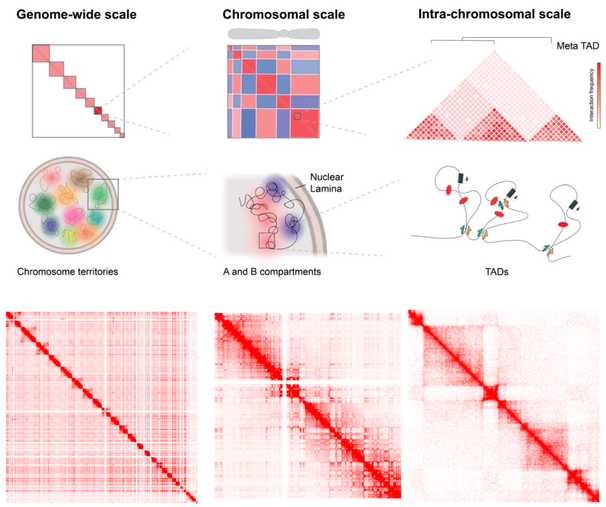

Fig.3 Distinct features observed in Hi-C maps

Hi-C contact maps visualize chromatin organization from a genome-wide scale to an intra-chromosomal scale. The genome-wide scale displays all 23 pairs of chromosomes. At a chromosomal scale, A and B compartments provide insight into chromatin conformation and gene expression. Within compartments, chromatin is organized into topologically associated domains (TADs) which are self-interacting regions that are highly conserved across cell types. Discrepancies in chromosome territories, A and B compartments, and TADs between wild type and reference genomes may highlight distinct chromatin organization features that contribute to differences in gene regulation.

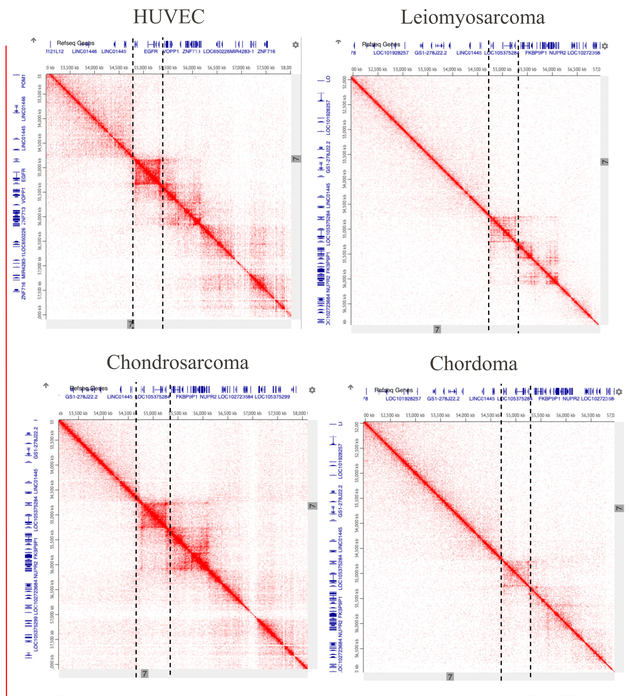

Fig.4 Conservation of chromosome organization around *EGFR* locus

Juicebox showed conservation of TAD structure within *EGFR* locus in cancerous tissue samples and non-cancerous cell line.

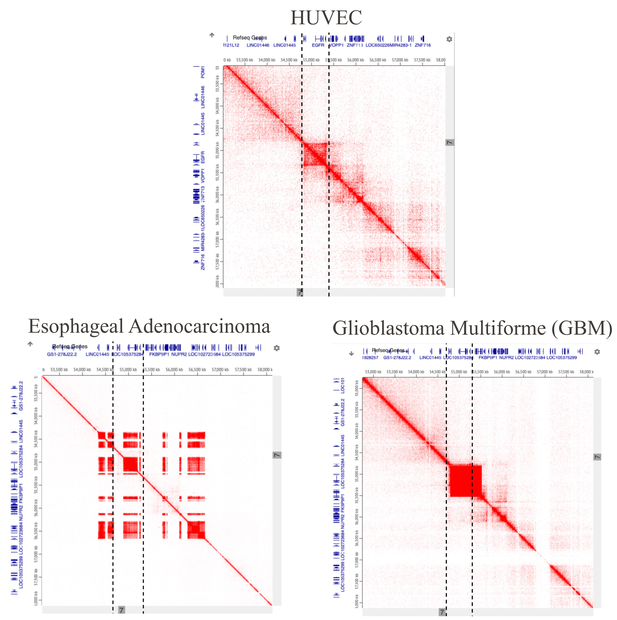

Fig.5 Differential chromosome organization around *EGFR* locus

Using Juicebox, structural variations were identified in the esophageal adenocarcinoma sample whereas focal amplification was identified in the GBM sample.

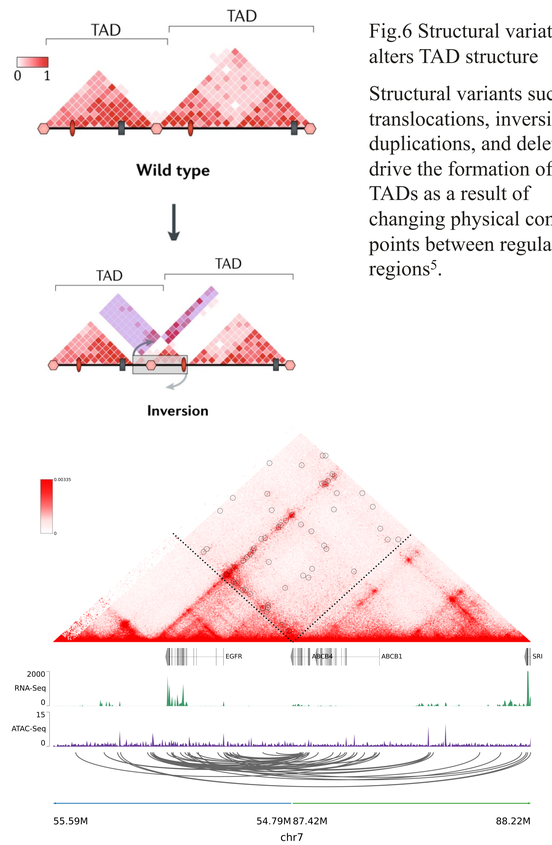

Fig.6 Structural variation alters TAD structure

Structural variants such as translocations, inversions, duplications, and deletions drive the formation of new TADs as a result of changing physical contact points between regulatory regions[5].

Fig. 7 In GBM sample, TAD formation reveals EGFR involvement with enhancer-hijacking event

Use of Neoloopfinder suggested that an inversion resulted in the formation of a new TAD, driving promoter-enhancer interaction between *EGFR* and previously distinct regulatory regions.

Conclusion

- Change in chromatin organization around *EGFR* was cancer specific and shown to influence *EGFR* expression.
- Further investigation will evaluate whether loop formations within the *EGFR* region are conserved in other cancer types.
- Understanding chromatin organization of *EGFR* may assist with development of new targeted therapies.

Acknowledgements

Bo Zhao, Lingqun Ye, Ellie Kim, and Kristy Mendoza

References

1) Cerami et al., Cancer Discovery 2012
2) Gao et al., Sci Signal 2013
2) Durand et al., Cell Systems 2016;3
3) Wang et al., Nat Methods. 2021
4) Mota-Gómez et al., Genes 2019;10
5) Spielmann et al., Nat Rev Genet 2018