**Media release from the University of Oslo**

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**A study of the epigenetics of breast cancer provides clues to mechanisms behind subtypes of the disease**

Breast cancer is caused by complex interactions between a patient-specific genetic background and our environment. Breast cancer cells undergo aberrant genome-wide DNA methylation at large in CpG rich areas known as CpG islands.

The newly identified methylated regions (CpGs) show remarkably and reproducibly conserved patterns of association to gene expression in the DNA from breast tumors in three independent breast cancer cohorts. These patterns result in two main signatures (clusters), one reflecting infiltrating immune cell signatures and another related to estrogen receptor signalling. These results indicate that, in at least some forms of cancer, aberrant DNA methylation occurs not as chaotic stochastic process but is precisely regulated. In fact, 80% of all CpGs that account for the associations in the estrogen receptor signalling cluster are found in enhancers - DNA segments controlling when and where genes are expressed.

The study is a close collaboration between the University of Oslo (project management and medical statistics), the Oslo University Hospital (sample and clinical data acquisition, tissue preparation, statistical and bioinformatic analysis), the Centre for Molecular Medicine Norway (NCMM) (functional studies and transcriptional bioinformatics) and Center National de Recherche en Génomique Humaine, France (data generation and epigenetic expertise).

Professor **Vessela Kristensen** from the University of Oslo, one of the lead investigators on the study, says: “These findings add significantly to our understanding of how estrogen receptor positive breast cancers develop from a luminal cell. As well as identifying new transcription factors, we have also confirmed the three main known drivers of estrogen receptor positive breast cancers. This methodology allows us to derive patterns also from the remaining tumour subtypes that should help us understand their origin better too, as well as which genes and mechanisms are involved.”

Around 70% of all cases of breast cancer are estrogen-receptor positive, meaning that the cancer cells have a particular protein (known as a receptor) that responds to the female sex hormone estrogen, enabling the tumour to grow. However, not all cancer cells carry this receptor – these are known as estrogen-receptor negative. The studies identified epigenetic regions specifically associated with either estrogen-receptor positive or estrogen-receptor negative breast cancer, underscoring the fact that these are biologically distinct cancers that develop differently.

**Thomas Fleischer**, senior scientist and shared first author, together with senior postdoc **Xavier Tekpli** at the Institute for Cancer Research, Radiumhospitalet comment: “Our new method identified enhancers whose DNA methylation is a key feature distinguishing the two main types of breast cancer (ER positive versus ER negative). When DNA methylation is a driving factor, we can apply this methodology to any cancer type to pinpoint transcription factors and enhancers involved in pathogenesis.”

Transcription factors (TFs) are key proteins binding to these DNA regions to control the rate of gene expression. We observed a strong enrichment for the binding of three critical breast cancer transcription factors: ESR1, GATA3 and FoxA1. Note that these TFs are known to be pivotal for the development of luminal disease. This allows us to dissect all the members of the involved pathways with unprecedented precision.

**Anthony Mathelier**, group leader at NCMM, leading the bioinformatics analysis of transcription factors commented: “This study highlights the importance of the alteration of gene transcription regulation in breast cancer subtypes through DNA methylation, controlling when and where genes are expressed. It is a very nice example of a strong collaboration between clinicians, experimental biologists, and computational biologists where the application of computational biology to clinical data derive new biological insights with potential impact for patients.”

By combining epigenetic data with other data from breast tissue (mRNA expression), the researchers were able to make plausible predictions of the genes for which their expression was targeted by differential DNA methylation at enhancer regions.

" It is wonderful to use statistical methods to discover signal hidden in clouds of noise, and to see the appearance of structure from complex data, structure that can then be interpreted as new molecular biology in cancer" says Professor **Arnoldo Frigessi**, leading the biostatical analyses.

**Anthoni Hurtado**, leading the functional studies adds that this study is one preliminary step to understand the how multiple ER chromatin interactions control the transcription of the estrogen target genes.

“This study takes the advantage of combining large scale transcriptomics with epigenomics data form breast tumors revealing new insights into the development and progression of these tumors The identified epigenetic regions specifically associated with either estrogen-receptor positive or estrogen-receptor negative breast cancer, underscore the fact that these are biologically distinct cancers that develop differently, and thus should be treated differently” adds **Anne-Lise Børresen-Dale**, professor emerita and founder of the Oslo Breast Cancer Consortium (OSBREAC) clinical material.

***Reference***

*Fleischer T., Tekpli X. et al. DNA methylation at enhancers identifies distinct breast cancer lineages. Nature Communications; 09 Nov 2017; DOI: 10.1038/s41467-017-00510-x.*

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**Major Institutions**

University of Oslo, Norway ([https://www.uio.no](https://www.uio.no/))

Oslo University Hospital, Norway ([https://www.ous.no](https://www.ous.no/))

Norwegian Cencer for Molecular Medicine, Norway ([www.](http://www.cancervic.org.au/) ncmm.no)

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the Norwegian Research Council ([https://www.forskningsradet.no](https://www.forskningsradet.no/))

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