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Day 1

Switching genes on and off in health and disease

Keynote speaker: *Doug Higgs*
University of Oxford, United Kingdom

Researchers now have access to over 100,000 human genomes and the genomes of an ever-increasing number of other organisms spanning the evolutionary tree of life. The next major task in biomedicine is to decode this information and provide a link between the DNA

MYCN promotes tumorigenesis by expanding E2F3a interactome(s) to multiple Histone Acetyl transferase complexes.

Speaker:

The developmental origins of infant leukaemia

Speaker: *Katrin Ottersbach*
University of Edinburgh, United Kingdom

Infant leukaemias are rare and very aggressive blood malignancies that affect children under the age of 1 and that have their origin in foetal development. They are most commonly associated with chromosomal rearrangements involving the MLL gene, which codes for a histone methyltransferase that is an important regulator in haematopoietic development. The translocation results in the generation of a fusion protein, the most frequent of which is MLL-AF4, which causes wide-spread epigenetic dysregulation and a general upregulation of transcription.
While MLL-AF4+ leukaemia in older children and adults requires additional, cooperating mutations, the MLL-AF4 fusion appears to be sufficient to drive the full leukaemic phenotype in infant patients. This suggests that the foetal origin is an important contributing factor.
My group has a long-standing interest in embryonic and foetal blood development and has, together with several other groups, over the years described a number of unique features of foetal blood progenitors that may contribute to the cells being more susceptible to MLL-AF4-mediated transformation. We have also recently reported how MLL-AF4 expression subverts normal blood development, resulting in the generation of a pre-leukaemic state. We have been able to define the developmental window and the likely cell(s)-of-origin in which this occurs. We have now transcriptionally further analysed these potential cells-of-origin and have defined a conserved foetal expression signature that persists in leukaemic blast cells and that is required for disease maintenance. This has demonstrated the dependency of the leukaemia on the presence and maintenance of foetal expressed genes and foetal epigenetic features, some of which may prove to be novel targets for therapy.

MYCN regulates the oncogenic activity of exosomes in neuroblastoma: potential role of PKM2

Presenter: *Alexia Tsakaneli*
Brunel University London, United Kingdom

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MYCN amplification is a key molecular aberration in high-risk neuroblastoma and predictive of poor outcome. In this study, we investigated the role of MYCN in regulating the protein cargo of exosomes, vesicles secreted by tumour cells that can be picked up by recipient cells with important functional consequences. Using a switchable MYCN system coupled to mass

EED-Targeted PROTACs Degrade EED, EZH2, and SUZ12 in the PRC2 Complex

Speaker: *Jessie Hsu*
Astra Zeneca, Boston, United States of America

Deregulation of the PRC2 complex, comprised of the core subunits EZH2, SUZ12, and EED, drives aberrant hypermethylation of H3K27 and tumorigenicity of many cancers. Although inhibitors of EZH2 have shown promising clinical activity, preclinical data suggest that resistance can be acquired through secondary mutations in EZH2 that abrogate drug target engagement. To address these limitations, we have designed several hetero-

The MLH1 polymorphism rs1800734 and risk of small bowel carcinomas with microsatellite instability

Presenter: *Laura Libera*
University of Insubria, Italy

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The *MLH1* promoter polymorphism -93G>A (rs1800734) is associated with microsatellite instability (MSI) in colorectal cancer (CRC) exhibiting *MLH1* promoter methylation. Recently, it has been proposed that BRAF/MAFG pathway may be driver of *MLH1* methylation in CRC1 and that rs1800734 influences methylation acquisition in *MLH1* promoter2.
Recently, *MLH1* hypermethylation and MSI have been demonstrated also in small bowel carcinomas (SBCs) at high frequencies3, but the role of rs1800734 has never been investigated in this site.
In this study, we genotyped *MLH1* rs1800734 (GG, GA and AA) in a well-characterized multicenter series of non-familial, non-ampullary SBCs (70 cases) and in a CRC cohort (300 cases) for comparison, in order to verify whether rs1800734 is associated with the risk of MSI-SBCs.
Among CRCs we observed MSI in 52/300 tumors (17,3%) that showed a significantly higher frequency of AA genotypes compared with MSS-CRCs (23% MSI-CRC vs 9% MSS-CRC, p=0.008). Interestingly, we found that AA patients developed CRCs at a significantly lower age than GA/GG patients (p=0.0017).
On the contrary, in SBCs we identified 25 (35.7%) MSI cancers (all with *MLH1* methylation); however, no significant association was found between MSI-SBCs and rs1800734 AA genotype (8% MSI-SBC vs 12% MSS-SBC). Moreover, no correlation was observed between rs1800734 and age of SBCs onset.
Our findings confirmed that rs1800734 risk allele is associated to MSI-CRC and seems to correlate with a possible accelerated tumorigenesis. By contrast, rs1800734 is not associated with a risk of MSI-SBC, suggesting that *MLH1* hypermethylation may occur by different mechanisms in SBC and CRC.

References

1. Fang et al. Mol Cell. 2014 Sep 18;55(6):904-915. doi: 10.1016/j.molcel.2014.08.010
2. Thomas et al. Sci Rep 2019 Sep 17;9(1):13463. doi: 10.1038/s41598-019-49952-x
3. Vanoli et al. Mod Pathol. 2017 Oct;30(10):1453-1466. doi: 10.1038/modpathol.2017.40

Two phases of hydroxymethylation changes during colon cancer progression. Should we target TETs?

Speaker: *Adele Murrell*
University of Bath, United Kingdom