Link found between cell identities and childhood cancer neuroblastoma

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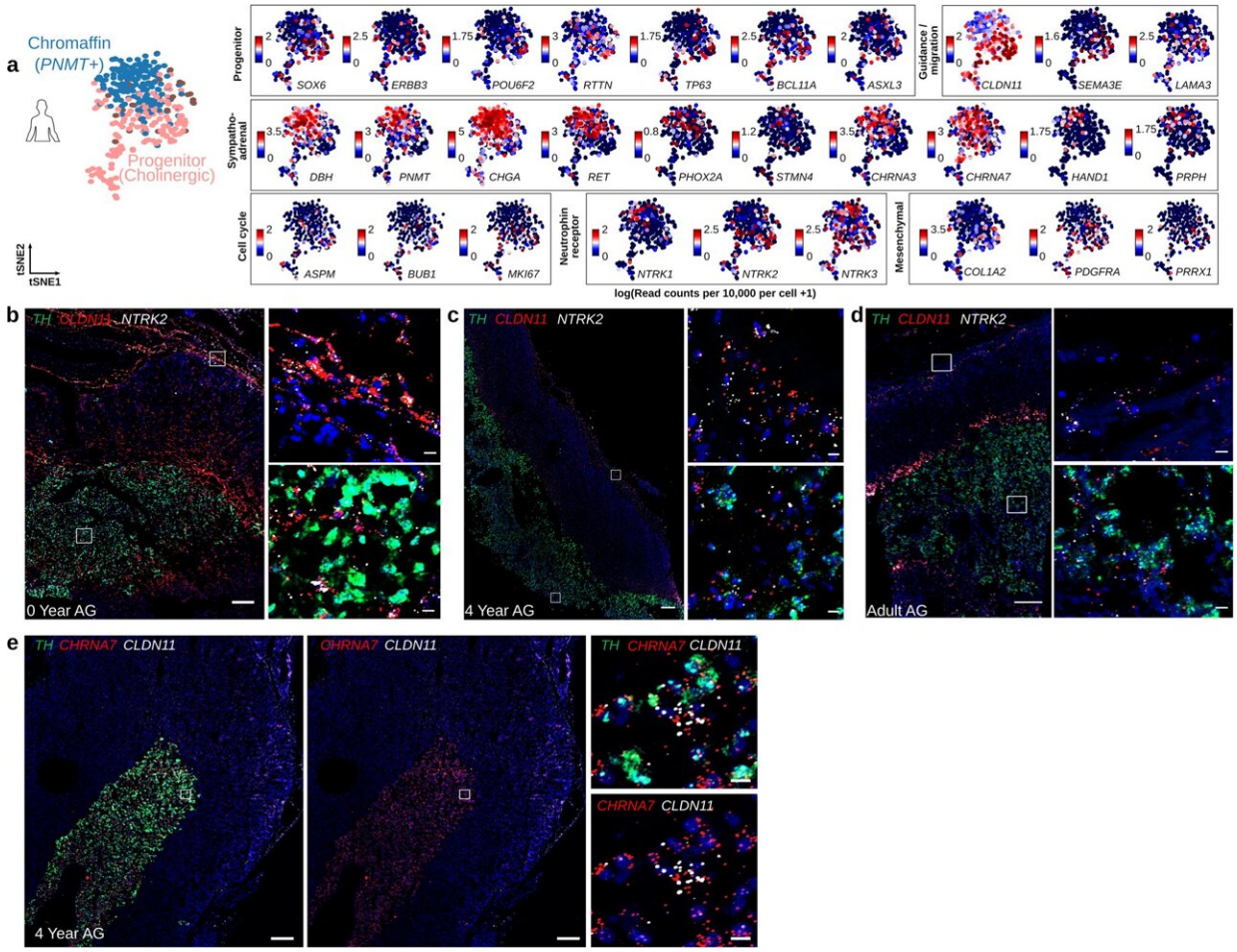

Location of human cholinergic progenitor (NTRK2+ CLDN11+) and chromaffin (TH+) cells within the postnatal human adrenal gland (AG). a tSNEs representing the expression of indicated genes in human cholinergic progenitor (pink) and chromaffin (blue) populations. The bars next to the tSNEs illustrate the expression measured as the logarithm of the read counts per 10,000. b–e

Overview of tile-scanned images (×20) of postnatal human adrenal glands (AG) at indicated age. Scalebar of overview: 200 μm, zoom of boxed image: 10 μm. b–d RNAscope in situ hybridization (ISH) for TH (green), CLDN11 (red), and NTRK2 (white) mRNA and counter stained with DAPI (blue). NTRK2+ CLDN11+ double positive cells were found in adrenal capsule and medulla exclusive from TH positive cells. e RNAscope ISH of a 4-year-old AG labeled with for TH (green), CHRNA7 (red), and CLDN11 (white) mRNA and nuclear counter-stain (DAPI) as indicated. For all RNAscope experiments, the signal distribution patterns and cell morphological features were shown by the different combination of probes and independently reproduced three times on different samples. Credit: DOI: 10.1038/s41467-021-24870-7

Neuroblastoma is a type of childhood cancer that develops in infants and young children. Whilst it is a relatively rare form of cancer, it is still responsible for approximately 15 percent of all cancer deaths in children. In a new study published today in *Nature Communications*, researchers at Karolinska Institutet have discovered that low-risk and high-risk neuroblastoma have different cell identities, which can affect the survival rate.

Neuroblastoma often starts in the sympathetic nervous system or the adrenal glands. This cancer has a high variability in outcome, ranging from spontaneous regression and complete disappearance to relentless disease progression with very few treatment options.

The child's age at the time of diagnosis is one of the most important prognostic factors for a favorable outcome. However, the importance of age is a question that has previously been left unanswered.

"In our research we have studied single cell sequencing in healthy adrenal tissues from fetuses, babies and older children, and compared this to tumor tissue from different neuroblastoma risk groups," says

Susanne Schlisio, associate professor at the Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, and co-corresponding author of the study.

Different cell types with different malignancy potentials

Tumor tissue samples have been collected from children where the age at diagnosis ranged from less than a month to 6,5 years. Approximately 50 percent of the tumors were classified as high-risk and 50 percent as low-risk.

"We discovered that low-risk and high-risk neuroblastoma tumors are composed of different cell types. The different cell types also showed to have a different malignancy potential," explains Susanne Schlisio.

The research group were able to match low-risk neuroblastoma to a cell type, which grows during the development of the fetal adrenal, while aggressive high-risk neuroblastoma matched a cell type that can only be found in children's adrenal tissue after birth.

Analyses of these cell types also revealed different gene expression programs that control the conditions for survival in correlation with age at diagnosis. Furthermore, the study shows that the cell type found in the adrenal tissue of children after birth has the characteristics of a progenitor cell, a form of a stem cell, which can develop into specialized cell types.

"These specialized cells can help to regenerate the healthy tissue after birth, but when they become abnormal and cancerous they may also be responsible for the aggressive neuroblastoma. This would explain why high-risk neuroblastoma arises in older children, and cannot be seen in

fetuses or very young babies, says Oscar Bedoya Reina, the study's first author and assistant professor at the Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet.

Increased understanding can contribute to less malignant tumors

The researchers will now expand their study in order to understand how the identified progenitor cell type further changes after birth to create specialized cell types.

"Understanding this progenitor cell type in detail, we might be able to make predictions and preliminary validations for future therapy strategies based on tumor differentiation. Discovering pathways that can lead to childhood tumors being less malignant will be important for the development of treatments that are currently non-existent for high-risk neuroblastoma, concludes Susanne Schlisio.

At the end of 2020, another study in the same field conducted by the Schlisio group, was published in the journal *Cancer Cell*.

More information: O. C. Bedoya-Reina et al, Single-nuclei transcriptomes from human adrenal gland reveal distinct cellular identities of low and high-risk neuroblastoma tumors, *Nature Communications* (2021). DOI: 10.1038/s41467-021-24870-7

Oscar C. Bedoya-Reina et al, Chromaffin Cells with Sympathoblast Signature: Too Similar to Keep Apart?, *Cancer Cell* (2020). DOI: 10.1016/j.ccell.2020.12.009

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