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Reporting Summary
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Statistics
For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

☐ The exact sample size (n) for each experimental group/condition, given as a discrete number and unit of measurement
☐ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐ The statistical test(s) used AND whether they are one- or two-sided
☐ Only common tests should be described solely by name; describe more complex techniques in the Methods section.
☐ A description of all covariates tested
☐ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐ For null hypothesis testing, the test statistic (e.g. F, t, r) with confidence intervals, effect sizes, degrees of freedom and P value noted. Give P values as exact values whenever suitable.
☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐ Estimates of effect sizes (e.g. Cohen’s d, Pearson’s r), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code
Policy information about availability of computer code

Data collection
A detailed description of the data and sample collection can be found in the methods section of the manuscript.

In synopsis:
DNA was isolated from 0.5 mL blood with the ReliaPrep chemistry (Promega) automated on the Freedom Evo Robot (Tecan). Next, genotyping was performed using the GSA-MDv3 array (Infinium, illumina) with a lab-specific clusterfile.

Peripheral blood mononuclear cells (PBMCs) and and bone marrow mononuclear cells (BM-MNCs) were isolated using optimized density gradient centrifugation. Thereafter, vials were transferred for long-term storage to liquid nitrogen, until further RNA-sequencing analysis. PBMC and MNC samples were prepped for scRNA-seq according to the 10X Genomics Chromium™ Single Cell 3’ v2 RNA sequencing specification. The generated cDNA was used for Illumina next-generation sequencing using a NextSeq500-v2 150 cycle kit with a sequencing depth of 25,000 reads/cell.

Within the PBMC fraction, classical monocytes were isolated using magnetic cell separation (microbeads, Mylteni biotec protocols) for functional analysis. The freshly isolated peripheral blood classical monocytes were stimulated with different stimuli to assess cytokine production capacity and ROS production, before and after radioactive iodine or surgical treatment.

Data analysis
For data analysis, we employed the statistical language R (version 4.0.3), FlowJo (version 10) and GraphPad Prism (version 8). A detailed description of this analysis can be found in the methods section of the manuscript. All code is made freely available on Github: https://github.com/CiiM-Bioinformatics-group/thyroid-cancer.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. Github). See the Nature Portfolio guidelines for submitting code & software for further information.
Data

Policy information about availability of data
All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:
- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy.

The single-cell transcriptomic and genotypic data generated in this study have been deposited at the European Genome-Phenome archive (EGA) under accession number EGAS00001005594. These data are available under restricted access; access can be obtained upon request. Targeted proteomics data generated in this study are provided as Supplementary information. Source data are provided with this paper.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research

Reporting on sex and gender
Our study included patients of both sexes and therefore applies to both sexes. Sexes were self-reported and later confirmed by DNA genotyping. In the study design, sex was included as a covariate to correct for this effect. Sex-specific analyses were not undertaken because of evidence for sex-specific effects in our study.

Population characteristics
The following patients groups were included in this study: patient with newly diagnosed thyroid carcinoma (metastatic or non-metastatic), patients with multinodular goiter receiving surgical or radioactive iodine treatment and healthy controls. General inclusion criteria: at least 18 years old and mentally competent

Criteria for exclusion were age <18 years, mental incompetence, pregnancy or breastfeeding, inflammatory or infectious diseases or an immunosuppressive status, use of medication interfering with the immune system (e.g. glucocorticosteroids, nonsteroidal anti-inflammatory drugs, cytostatics) diagnosis of clinical thyroid dysfunction at time of inclusion, reduced platelet counts or other conditions associated with an increased risk of bleeding, severe comorbidities such as other active malignancies (except for basal cell carcinoma), serious psychiatric pathology and a self-reported alcohol consumption of >21 units per week

Recruitment
Consecutive patients with multinodular goiter or newly diagnosed thyroid cancer visiting our center between March 2018 and November 2019 were recruited.

Ethics oversight
Ethical approval CMO Arnhem-Nijmegen

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☑ Life sciences
☐ Behavioural & social sciences
☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size
No statistical tests were undertaken to determine the sample size a priori, and sample sizes were limited by clinical availability. Due to the invasive investigations, the risks and burden on participants was carefully taken into account. Sample size of the current study was deemed sufficient to detect effects statistically.

Data exclusions
No data were excluded in any of the analysis. Of note, for some of the immunological assays performed, not enough biological material was available for some of the patients, and subsequently the final number of tests may differ for the various assessments

Data removed for quality control reasons are stated in the Methods section.

Replication
Cytokine assays were performed on duplicates, ROS assays on triplicates. Reported results were consistent across these biological replicates.

To reduce inter-assay variation, cytokine assays and proteomics analysis were performed in one batch. To control for inter-plate variation, bridging samples were taken along for cytokine assays and proteomics analysis. Variability between plates was minimal. Flow cytometry validation was used to validate the single-cell RNA sequencing cell population frequencies.

Randomization
This study contained healthy individuals, multi-nodal goiter patients and thyroid cancer patients. There was no randomization between these...
Randomization groups. During inclusion we aimed to distribute, age, gender and BMI between the three groups as comparable as good as practically possible and corrected for age and gender as stated in the manuscript.

Blinding All experiments were conducted in an unblinded way since the investigators were involved in the planning, execution and analyses of the current study.

**Reporting for specific materials, systems and methods**

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

### Materials & experimental systems

| n/a | Involved in the study |
|-----|-----------------------|
|     | Antibodies            |
| X   | Eukaryotic cell lines |
|     | Palaeontology and archaeology |
| X   | Animals and other organisms |
|     | Clinical data         |
|     | Dual use research of concern |

### Methods

| n/a | Involved in the study |
|-----|-----------------------|
|     | ChIP-seq              |
|     | Flow cytometry        |
| X   | MRI-based neuroimaging |

#### Antibodies

| Antibodies used | Name | article number | firma | Lot |
|----------------|------|----------------|-------|-----|
| FITC anti-human CD45RA Antibody | 304105 | Biolegend | B242180 |
| PerCP anti-human CD45 Antibody | 304025 | Biolegend | B242998 |
| Brilliant Violet 785™ anti-human CD123 Antibody | 306031 | Biolegend | B253033 |
| APC/Cyanine7 anti-human CD3 Antibody | 317341 | Biolegend | B275534 |
| APC/Cyanine7 anti-human CD19 Antibody | 363009 | Biolegend | B276796 |
| APC/Fire™ 750 anti-human CD15 (SSEA-1) Antibody | 323041 | Biolegend | B283027 |
| APC anti-human CD10 Antibody | 312209 | Biolegend |
| PE-CFS94 Mouse Anti-Human CD110, clone 1.6.1 562416 | BD Biosciences |
| PE anti-human CD90 (Thy1) Antibody | 328109 | Biolegend |
| Brilliant Violet 510™ anti-human CD38 Antibody | 356611 | Biolegend |

Validation all antibodies were validated for the species and application as validated by the manufacturer (see manufacturer’s website)

#### Eukaryotic cell lines

**Policy information about cell lines and Sex and Gender in Research**

| Cell line source(s) | TPC-1 is a widely published and well-characterized cell line isolated from a papillary thyroid carcinoma of a female patient. |
| Authentication       | The cell line was not authenticated. |
| Mycoplasma contamination | All cell lines tested negative for mycoplasma contamination. |
| Commonly misidentified lines (See ICLAC register) | N/A |

#### Clinical data

**Policy information about clinical studies**

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

| Clinical trial registration | ClinicalTrials.gov identifier: NCT03397238 |
| Study protocol | The study was approved by the local Ethics Committee (Ethical approval CMO Arnhem-Nijmegen 2017-3628). The complete study protocol is available from the corresponding author, [R.M.], upon reasonable request. Study information is also registered at ClinicalTrials.gov (NCT03397238). |
| Data collection | This study includes samples of subjects who participated in the observational trial "Myeloid Cell Reprogramming in Thyroid Carcinoma" between March 2018 and November 2019. |
Outcomes

Our study is an observational study examining primary the transcriptional and functional reprogramming of myeloid cells, and secondary the change of functional reprogramming after RAI treatment was assessed.

Flow Cytometry

Plots

Confirm that:
- The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- All plots are contour plots with outliers or pseudocolor plots.
- A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation

Bone marrow-derived mononuclear cells were freshly isolated by Ficoll density gradient and cryopreserved until analysis. Cell populations in BM-MNCs were identified with the FACS Aria III (Becton Dickinson, Franklin Lakes, NJ, USA). 10x10^6 cells were washed in PBA (0.5% BSA in PBS) after thawing, blocked with Fc-block (Miltenyi Biotec, Bergisch Gladbach, Germany), stained for 45 min at 4°C in the dark with the monoclonal antibodies.

Instrument

Becton Dickinson FACS Aria III

Software

BD Diva software was used to collect and FlowJo v10 to analyze the data.

Cell population abundance

Cell sorting not employed

Gating strategy

Compensation was performed using single stains with compensation beads. For each sample, at least 500,000 counts were recorded. A gate was previously designed based on forward and side scatter to remove debris from analysis.

Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.