Multi stage differentiation defines melanoma subtypes…

Figure 1

* Sequencing of 53 melanoma cell lines
* Clustering into 4 robust clusters with significantly different gene expression (A und B)
* Distinct clusters in PCA (C)
* Comparison with a publicated set of an in vitro melanocyte differentiation model (Micah 2013) (D, oben)
* Projection of the identified clusters within the pre-defined space (D, unten) 🡪 Clusters resemble different differentiation states
* Clusters are associated with differentiation associated pathways (E)
* Marker genes corroborate the identified clusters as 4 substages of melanoma (F)
* Enrichment of MITF target genes in melanocytic vs transitory phenotype (G)

Figure 2

* Melanoma cell lines in their parent stage (P) and resistant stage (R) are shown. 2 different resistance mechanisms are shown
* Resistance is defined as resistance to vemurafenib
  + RTK upregulation
  + MAPK reactivation
* Cell lines with an RTK upregulation resistance mechanism to BRAF/MEK inhibitor treatment show a dedifferentiation correlated with resistance
* Cell lines with a MAPK reactivation do not show this dedifferentiation (A)
* Treatment with vemurafenib lead to stepwise dedifferentiation in both types of cells (RTK up and MAPK reactivation) (B)
  + A transient dedifferentiation might also be present which is later lost in M397
  + The stable dedifferentiation state is associated with a loss of SOX10 by epigenetic mechanisms (Shaffer et al 2017) (B)
* C: time after Vemurafenib treatment and associated dedifferentiation
* Supplementary material: the dedifferentiation process was confirmed in patients during treatment and upon progression
* The same pattern of dedifferentiation is shown for IO treatment (which has been demonstrated before due to loss of immunogenic antigens during dedifferentiation) (D)

Im weiteren wurden die Daten noch durch TCGA Proben und Machine learning classification untermauert, sodass die Subtypes als sehr robust angenommen werden können.

Außerdem wurden Methylierungschanges angeschaut, die als mitursächlich für die Transkriptionschanges im Prozess der Dedifferenzierung identifiziert wurden.

Am Ende gibt es noch einen Treatment-Vorschlag mit Ferroptose-Induktion, da dedifferenzierte Zellen anfälliger dafür sind.