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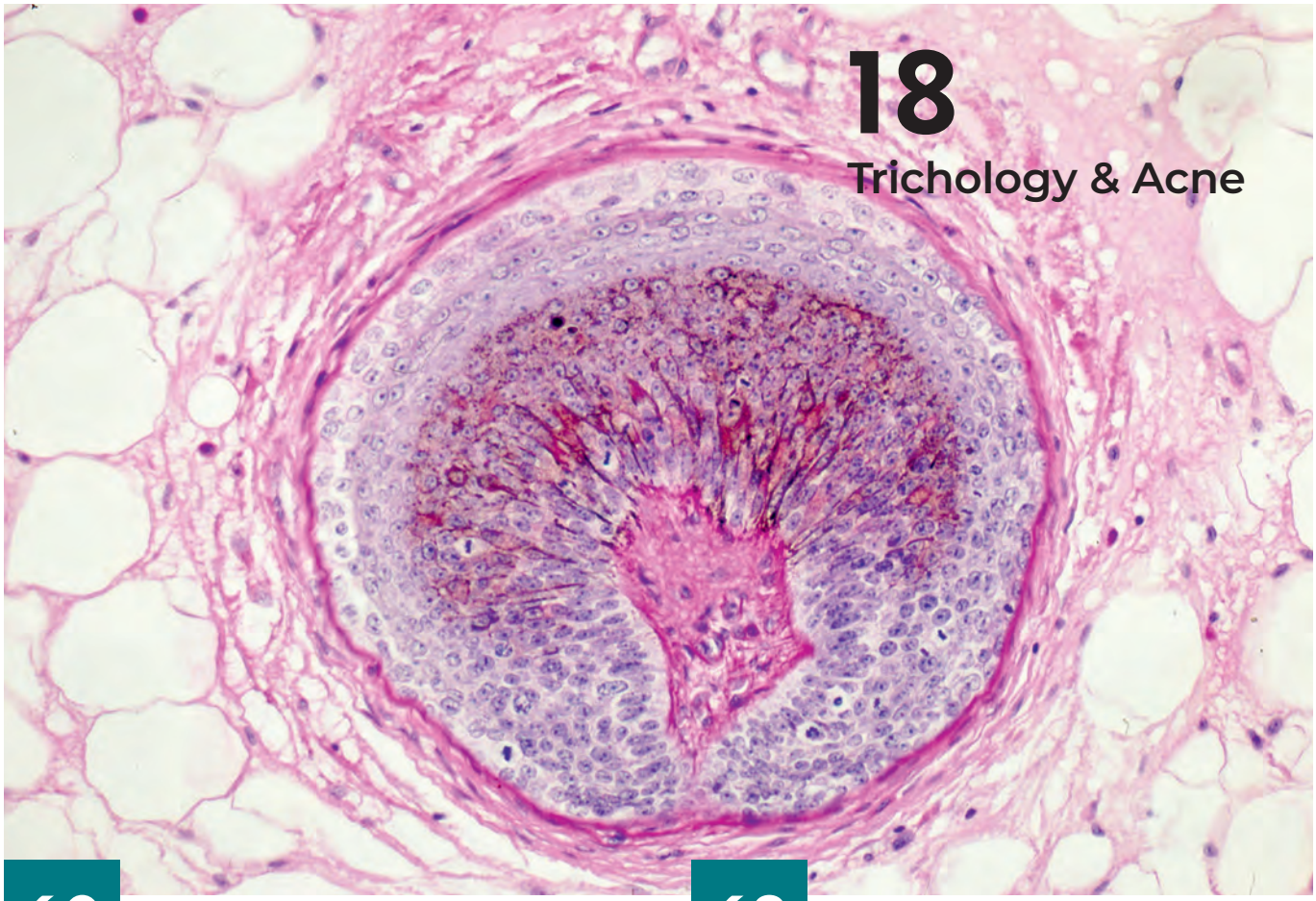

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WHAT'S NEW

Escape from NK cell tumor surveillance by NGFR-induced lipid remodeling in melanoma

This section is a contribution from the SKINTEGRITY.CH collaborative research consortium. The present work was performed by Dr. Julia Lehmann and colleagues in the research group of Prof. Lukas Sommer, co-director and one of the principal investigators of the initiative, with SKINTEGRITY.CH colleagues Profs. Mitchell Levesque, Reinhard Dummer, and Christian Stockmann and co-workers.

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Julia Lehmann. Metastasis is the primary cause of death for cancer patients. Particularly, cutaneous melanoma, the deadliest form of skin cancer, is characterized by its ability to metastasize already at early stages of tumor development. A critical feature of metastasis formation is the evasion of tumor cells from the constant anti-cancer surveillance by the immune system. A recent study by Lehmann et al. in Science Advances sheds new light on the immune evasion strategies used by human melanoma cells. The study demonstrates that melanoma cells expressing the neural crest stem cell marker NGFR (CD271/p75^{NTR}) can evade tumor recognition and killing by natural killer (NK) cells. NGFR expression in melanoma is linked to aggressive subpopulations associated with metastasis formation and therapy resistance. Notably, in the present study, the authors found that overexpression of NGFR in human melanoma cells leads to increased metastasis formation in a mouse model with adoptively transferred human NK cells. This suggests that evasion from NK cells is a crucial process by which NGFR^{high} melanoma cells promote metastasis.

Mechanistically, the study shows that NGFR downregulates activating NK cell ligands and upregulates the fatty acid stearoyl–coenzyme A desaturase (SCD) in melanoma cells *(Fig. 1)*. Notably, pharmacological or small interfering RNA-mediated blocking of SCD successfully restored impaired NK cell-mediated killing of NGFR^{high} mel-

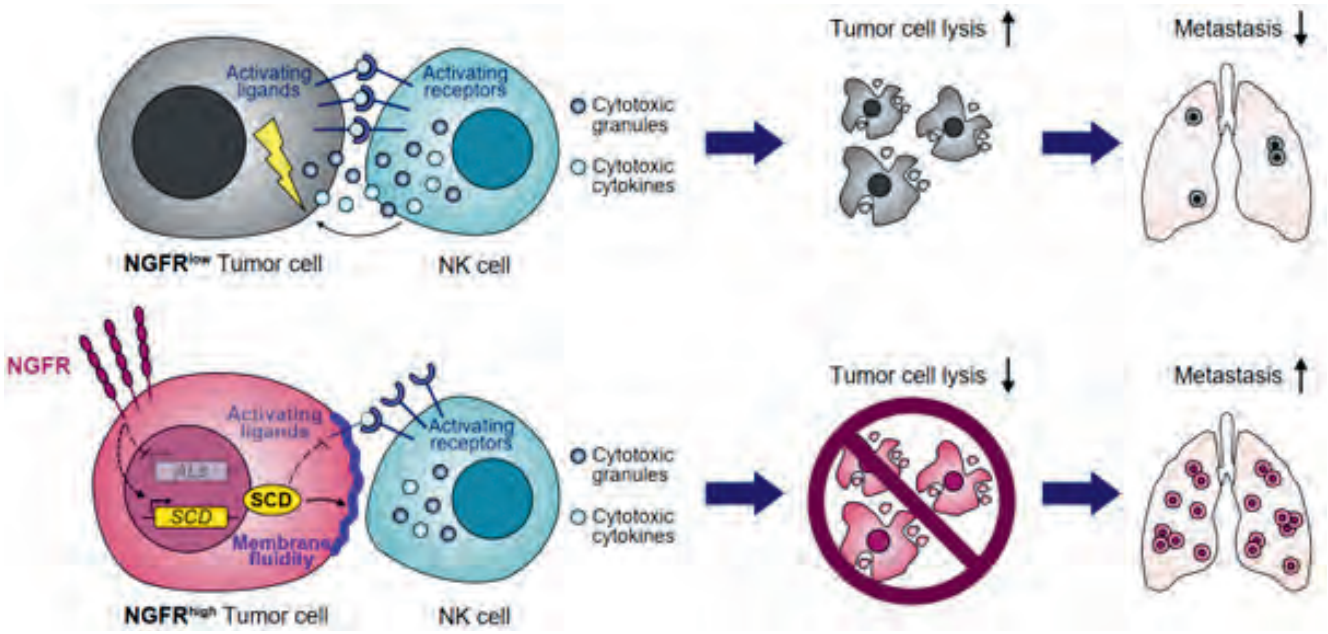

Figure 1: Model summarizing the findings of the study. Upper part: An NGFR^{low} tumor cell gets recognized by an NK cell via activating receptors binding to the respective activating ligands on the tumor cell. This leads to efficient NK cell-mediated tumor cell lysis and, consequently, diminished metastasis formation. Lower part: An NGFR^{high} tumor cell bypasses recognition and lysis by NK cells, which ultimately results in increased metastasis formation. Mechanistically, NGFR decreases gene expression of NK cell-activating ligands (ALs) and upregulates SCD. SCD impairs presentation of activating ligands on the tumor cell surface and increases plasma membrane fluidity – both potential immune control antagonizing pathways that protect melanoma cells from NK cell clearance and ultimately promote metastasis formation. (NGFR, nerve growth factor receptor; SCD, stearoyl-coenzyme A desaturase; ALs, activating ligands). Illustration from Lehmann et al., 2023.

anoma cells in vitro and in vivo. SCD regulates fatty acid desaturation and thereby controls cell membrane fluidity. Consistent with this, NGFR overexpression in melanoma cells resulted in increased cell membrane fluidity, which could be reverted by SCD inhibition. SCD also appeared to regulate the presentation of ligands for activating NK cell receptors on the tumor cell surface *(Fig. 1)*. Therefore, the authors propose that NGFR-induced SCD protects melanoma cells from NK cell clearance both by suppressing NK cell-activating ligands and by increasing cell membrane fluidity. Moreover, the work suggests that SCD-induced lipid remodeling is a specific mechanism by which NGFR protects tumor cells from NK cell surveillance, ultimately promoting metastatic disease.

In summary, this study provides new insights into the complex molecular mechanisms underlying melanoma metastasis and identifies NGFR as a critical mediator of innate immune evasion. As NK cells play a crucial role in combatting metastatic spread and are emerging as attractive targets for immunotherapy, the study's findings may help in the development of more effective therapies for this aggressive type of cancer.

Referenz

Escape from NK cell tumor surveillance by NGFR-induced lipid remodeling in melanoma
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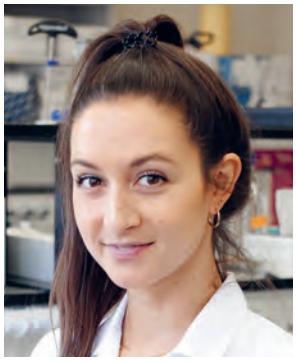

Dr. sc. nat. Julia Lehmann

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Colourful Feathering of a Peacock (Symbolic Picture)