EVBO Paper-of-the-month - February 2024

Jakab M, Lee KH, Uvarovskii A, Ovchinnikova S, Kulkarni SR, Jakab S, Rostalski T, Spegg C, Anders S, Augustin HG. Lung endothelium exploits susceptible tumor cell states to instruct metastatic latency. *Nat Cancer.* 2024 Feb 2. doi: 10.1038/s43018-023-00716-7.

Metastasis is the fatal hallmark of cancer, although representing a highly inefficient biological process. During metastasis, cancer cells hijack blood vessels and travel via the circulation to colonize distant sites, while closely interacting with endothelial cells (EC) throughout the various steps of dissemination. Due to the rarity of metastasis, a novel experimental strategy to enrich specifically for metastasizing tumor cell (mTC) subpopulations capturing all cell states of the early colonization process was developed. In combination with single-cell RNA-sequencing, a first blueprint of the transcriptional basis of early mTC decisions was generated and the temporal interactome of mTCs with lung ECs was resolved. Upon their arrest at the metastatic site, TCs either started proliferating intravascularly or extravasated and preferably reached a state of quiescence. Homeostatic endothelial-derived angiocrine Wnt factors were found to drive this bifurcation by inducing a mesenchymal-like phenotype instructing mTCs to follow the extravasation-dormancy route. In-depth analyses of the single-cell data revealed that the responsiveness of mTCs towards angiocrine Wnt signaling was not regulated at the receptor-ligand level. Moreover, in vivo niche-labeling approaches identified that latent and proliferative TCs occupied the same vascular niches and that the endothelium elicited a bimodal response toward the tumor challenge. This was marked by focal upregulation of biosynthesis genes and matrix remodeling events in the physical vascular micro-niche of proliferating TCs but not latent TCs, and the systemic upregulation of immune-regulatory angiocrine factors. Surprisingly, morphologically homogenous TCs displayed unexpected baseline transcriptional heterogeneity in culture, which was established at the epigenetic level and served as the impetus of mTC behavior. Epigenetically plastic cells were marked by high Wnt signaling activity and a mesenchymal-like state, leading them to preferably follow the extravasation-dormancy route. Epigenetically sealed TCs had low activity and proliferated intravascularly. Collectively, the data identified the predetermined methylation status of disseminated TCs as a key regulator of mTC behavior in the metastatic niche. While metastatic niche-derived factors per default instruct the acquisition of quiescence, mTCs unwind a default proliferation program and only deviate from it if epigenetic plasticity renders them responsive toward the microenvironment.