CAF Tracks: adhesive EV-Like structures linking stromal senescence to tumor adaptation

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Cancer-associated fibroblasts (CAFs) are key architects of the tumor microenvironment, regulating cancer progression and therapeutic response. While extracellular vesicles (EVs) are established mediators of stromal-cancer communication, their contribution has largely been framed around released, diffusible entities, leaving matrix-bound modes of extracellular signalling poorly defined.

Recently, we identified CAF-derived "tracks" as a previously overlooked class of adhesive, EV-like tubular extracellular structures deposited during fibroblast migration. In contrast to canonical EVs, tracks originate from integrin β5-enriched adhesive domains of migrating fibroblasts that are retained at the trailing edge and left behind within the extracellular matrix, preserving the spatial footprint of fibroblast migration. Track deposition is markedly increased in response to therapy, which induces a senescent-like status in CAFs. Given that cancer cells adhere to, migrate along, and internalize track material, we investigated whether tracks represent a novel, therapy-regulated mode of intercellular communication within the tumor microenvironment.

Bioinformatic analysis of a colorectal cancer single-cell atlas reveals that integrin β5 expression, a key component of track formation, is largely restricted to the stromal compartment and is particularly elevated in CAF populations from metastatic samples, linking β5-high fibroblast states to aggressive disease contexts. Additionally, proteomic profiling shows that CAF-tracks undergo therapy-associated remodelling characterized by increased abundance of stress-response and immunosuppressive factors, such as B7-H3 and PD-L1. This therapy-dependent signature is consistent with tracks representing a spatially confined extension of the senescence-associated secretory phenotype (SASP) embedded within adhesive extracellular material. Lastly, reflecting the potential functional consequences of these tubular EV-like structures, cancer cells exposed to tracks exhibit broad transcriptional reprogramming, with indications of altered metabolism, epithelial-mesenchymal plasticity, and cellular stress/ survival responses.

Collectively, these findings support CAF-derived tracks as therapy-responsive, matrix-bound EV-like structures associated with metastatic stromal states and cancer cell reprogramming, suggesting that fibroblast migration may generate a spatially organized mode of stromal communication that contributes to tumor progression and adaptation to therapy.