Review of: "Reprogrammed Schwann Cells Organize into Dynamic Tracks that Promote Pancreatic Cancer Invasion"

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Participation of Schwann cells (SC) in solid tumor growth and progression (spreading and metastasis formation) has been recently demonstrated in both in vitro and in vivo models in experimental animals and humans. SC have been reported to stimulate malignant cell motility, invasiveness, EMT and formation of “tunnel”-like structures to attract migrating tumor cells and direct their spreading. Activation of SC in the tumor microenvironment has been shown to induce their denervation, dedifferentiation and releasing of cytokines, chemokines and growth factors, which affect different cell populations including malignant cells and infiltrating immune cells. Importantly, using functional, morphological and molecular approaches, several teams have provided evidence that allowed suggesting that tumor-induced modulation of SC has many aspects of and similar signaling pathways with Wallerian degeneration. Wallerian degeneration is a physiological response to the peripheral nervous system lesion aiming at degeneration of the distal end of a traumatized axon and further guiding nerve fiber regeneration, where activated SC, or repair SC, play a key role at all stages of the process. Furthermore, comparative analysis of neurotrauma-activated SC – repair SC, and tumor-activated SC confirmed their functional and gene-expression signature similarity, which allows the implication of ‘repair-like’ SC term for tumor-associated SC. Finally, recent studies revealed that tumor-activated SC actively attract immune regulatory cells and up-regulate their immunosuppressive activity. However, in spite of noticeable progress in tumor-associated SC research, mechanistical and functional studies investigating SC and tumor cell interactions to identify specific factors responsible for SC activation and pathways utilized by SC to support tumor cell spreading are still limited.

“Reprogrammed Schwann Cells Organize into Dynamic Tracks that Promote Pancreatic Cancer Invasion” paper by Sylvie Deborde et al is an excellent continuation of research toward better understanding of the clinical aspects of the tumor neuroenvironment. Combining bioinformatic, experimental and pre-clinical approaches, authors presented not only strong confirmatory data, which is very important, but a lot of new basic and translational results that explain how SC function in the tumor milieu. First, testing the correlation between the SC signature scores and clinical outcomes in patients with pancreatic cancer, authors revealed significant correlations with higher scores corresponding to worse outcomes. In vitro co-culture studies with the SC cell line and tumor cell line partly confirmed conclusions obtained from the dataset analysis. Although this in vitro part could be expanded to cover a wider range of cellular interactions affecting SC signature scores, it links clinical in vivo results with model in vitro findings to stress their clinical significance. Combination of clinical in vitro and animal in vivo approaches is effectively developed in the next parts of the paper. Second, IHC and morphometric analyses of human tumor specimens, examination of tumor cell migration patterns after

injection into sciatic nerve in mice and evaluation of SC interaction with cancerous cells in the chemotactic chambers demonstrated that SC could reorganize malignant cells into chains and produce paths for their migration. The authors termed these clusters ‘Tumor Activated Schwann cell Tracks (TASTs)’. Several unique cellular model systems were used to understand and verify unusual orchestration of SC-tumor cell interactions, which results in architecting TASTs and supporting tumor cell invasiveness. SC have been proven to organize into dynamic tracks and wrapped themselves around tumor cells to form these tracks. In turn, this permitted tumor cell to pass through when SC directly applied forces on the cancerous cells. These new findings would open additional opportunities not only for the tumor microenvironment research but also for tissue regeneration studies where both wound healing and Wallerian degeneration pathways are closely intersected.

Third, the results of in vitro and in vivo c-Jun knockout experiments demonstrated an essential role of c-Jun signaling in the three-dimensional self-organized linear structures of SC, which operate as unique paths for directing tumor cell migration. SC c-Jun has been shown to regulate intracellular actin re-organization and modify physical properties of SC. C-Jun facilitated SC to cover tumor cells imitating the microtunnels and create tracks encouraging guiding passage for malignant cells. Furthermore, utilization of the JNK inhibitors revealed that c-Jun activity in SC can be effectively targeted by pharmacological agents. This is important since a direct proof that targeting the tumor neuroenvironment may have a therapeutic applicability for controlling cancer progression, at least in terms of perineural invasion, has been anticipated for a long time.

Finally, the results of the paper offer obvious and interesting directions for future analyses of the tumor neuroenvironment. These include but are not limited to the testing of cancer-specific aspects of the cross-talk between SC and different mouse and human tumor cell lines; uncovering receptors and signaling pathways in malignant cells affected by repair and ‘repair-like’ SC; understanding how ‘repair-like’ SC affect non-malignant cells, like normal epithelial cells or immune cells; and identification and pre-clinical testing of SC-specific pharmacological agents or biological molecules that can target SC activity of differentiation stage in the different environment, including the tumor macro- and microenvironment.