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# Interactions between Schwann cells and metastatic breast carcinoma: contact-dependent and independent effects

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**Abstract**

Schwann cells and may enhance cancer growth and metastasis. Breast carcinoma is a heterogeneous disease and our previous studies demonstrated further heterogeneity in site-dependent metastasis. Specifically cells isolated from liver metastasis of 4T1 mammary carcinoma cells (4TLM) demonstrate distinct phenotypic features leading to diverse tumor microenvironment compared to 4T1 mammary carcinoma cells metastasized to brain (4TBM). In accordance, non-metastatic/hardly metastatic cells obtained from 4T1 mammary carcinoma (67NR cells) interacts with their microenvironment differently. Hence, we examined the effects of secretomes obtained from 67NR, 4TBM and 4TLM cells on primary Schwann cells obtained from mouse sciatic nerve, specifically focusing on inflammatory cytokine release. Secretomes of liver metastatic subset of mammary carcinoma cells (4TLM) induced striking increases in IL-6 secretion, which was markedly higher than IL-6 secretion induced by secretomes of 4TBM and 67NR cells. Similarly, only 4TLM secretomes induced remarkable increases in inflammatory chemokines KC and MIP-2. Monocyte Chemoattractant Protein-1 (MCP-1) (also called CCL2), involved in migration of monocyte, is highly secreted by 4TLM cells but not by 4TBM and 67NR cells. Secretomes of 4TLM cells also induced robust increases in MCP-1 secretion from Schwann cells. Interestingly metastatic cells decreased IL-1b secretion from Schwann cells.

Next we determined how co-culturing of Schwann cells with carcinoma cells alter cytokine/chemokine secretion in order to determine contact-dependent changes. Schwann cells were co-cultured with cancer cells at 1/5, ½.5 and 1/1 ratio and secretomes were analyzed for cytokine secretion. Interestingly, co-culturing markedly suppressed IL-6 secretion from Schwann cells. Secretion of chemokines such as KC and MCP-1, however increased following co-culturing.

Lastly we have performed proteomic analysis of Schwann cell secretomes in the presence and absence of secretomes from cancer cells. Peptides were analyzed using the Orbitrap Fusion mass spectrometry instrument (Thermo Scientific) coupled with the Dionex Ultimate 3000 RSLCnano system. For bioinformatics analysis, the Proteome Discoverer (PD) program was used. As the Venn diagram shows, 446 proteins were identified in secretomes of unstimulated Schwann cells. Interestingly 363 of these proteins were also found in metastatic and non-metastatic breast cancer cells. This was surprising given the differences in cell lineages. Analysis of the 363 common proteins by KEGG pathways revealed several important carcinoma-associated pathways, such as the HIF-1 signaling pathway. The 37 proteins unique to Schwann cells pointed out two reactome pathways: Regulation of Insulin-like Growth Factor transport and post-translational protein phosphorylation. Protein content of secretomes of Schwann cells stimulated with secretomes of cancer cells differed from unstimulated Schwann cells such that 13 proteins were markedly downregulated while over 200 proteins were upregulated. We are in process of analyzing these results.