Identification of potential chemical substrates as fuel for hypoxic tumors that may be linked to invadopodium formation in hypoxia-induced MDA-MB-231 breast-cancer cell line

ABSTRACT

Hypoxia plays a significant role in solid tumors by the increased expression of hypoxia-inducible factor-1α (HIF-1α), which is known to promote cancer invasion and metastasis. Cancer-cell invasion dynamically begins with the degradation of the extracellular matrix (ECM) via invadopodia formation. The chemical substrates that are utilized by hypoxic cells as fuel to drive invadopodia formation are still not fully understood. Therefore, the aim of the study was to maintain MDA-MB-231 cells under hypoxia conditions to allow cells to form a large number of invadopodia as a model, followed by identifying their nutrient utilization. The results of the study revealed an increase in the number of cells forming invadopodia under hypoxia conditions. Moreover, Western blot analysis confirmed that essential proteins for hypoxia and invadopodia, including HIF-1α, vascular endothelial growth factor (VEGF), metallopeptidase-2 (MMP-2), and Rho guanine nucleotide exchange factor 7 (β-PIX), significantly increased under hypoxia. Interestingly, phenotype microarray showed that only 11 chemical substrates from 367 types of substrates were significantly metabolized in hypoxia compared to in normoxia. This is thought to be fuel for hypoxia to drive the invasion process. In conclusion, we found 11 chemical substrates that could have potential energy sources for hypoxia-induced invadopodia formation of these cells. This may in part be a target in the hypoxic tumor and invadopodia formation. Additionally, these findings can be used as potential carrier targets in cancer-drug discovery, such as the usage of dextrin.

Keyword: Cancer invasion; Invadopodia; ECM; Hypoxia; HIF-1α; Phenotype microarray