Scientific Paper:

PNAS (2016) vol. 113, no. 33, 9292-9297

Intratumoral oxygen gradients mediate sarcoma cell invasion

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Abstract:

Hypoxia is a critical factor in the progression and metastasis of many cancers, including soft tissue sarcomas. Frequently, oxygen (O_2) gradients develop in tumors as they grow beyond their vascular supply, leading to heterogeneous areas of O_2 depletion. Here, we report the impact of hypoxic O_2 gradients on sarcoma cell invasion and migration. O_2 gradient measurements showed that large sarcoma mouse tumors (> 300 mm^3) contain a severely hypoxic core [≤ 0.1 % partial pressure of O_2 (pO_2)] whereas smaller tumors possessed hypoxic gradients throughout the tumor mass ($0.1 - 6$ % pO_2). To analyse tumor invasion, we used O_2-controllable hydrogels to recreate the physiopathological O_2 levels in vitro. Small tumor grafts encapsulated in the hydrogels revealed increased invasion that was both faster and extended over a longer distance in the hypoxic hydrogels compared with nonhypoxic hydrogels. To model the effect of the O_2 gradient accurately, we examined individual sarcoma cells embedded in the O_2-controllable hydrogel. We observed that hypoxic gradients guide sarcoma cell motility and matrix remodelling through hypoxia-inducible factor-1α (HIF-α) activation. We further found that in the hypoxic gradient, individual cells migrate more quickly, across longer distances, and in the direction of increasing O_2 tension. Treatment with minoxidil, an inhibitor of hypoxia-induced sarcoma metastasis, abrogated cell migration and matrix remodelling in the hypoxic gradient. Overall, we show that O_2 acts as a 3D physicotactic agent during sarcoma tumor invasion and propose the O_2-controllable hydrogels as a predictive system to study early stages of the metastatic process and therapeutic targets.

Keywords: hydrogel, sarcoma, hypoxia, gradients, migration