Incremental hypoxia inside the growing tumor mass drives epigenetic drug resistance by activating non-genetic repair of anti-apoptotic DNA, which could be impaired by drug treatment. Hence, rescuing inter-tumor hypoxia by oxygen-generating microparticles may promote susceptibility to anti-tumor drugs. Moreover, a tumor-on-a-chip model a enables user-specified alternation of clinic-derived samples. This study utilized patient-derived glioblastoma tissue to generate cell spheroids with size variations in a 3D microchannel network chip (Glioblastoma chip). As the spheroid size increased, epigenetic drug resistance was promoted with inward hypoxia severance, as supported by the spheroid size-proportional expression of hypoxia-inducible factor-1a in the chip. Loading anti-hypoxia microparticles onto the spheroid surface significantly reduced drug resistance by silencing the expression of critical epigenetic factor, resulting in significantly decreased cell invasiveness. The results were confirmed in vitro using cell line and patient samples in the chip as well as chip implantation into a hypoxic hindlimb ischemia model in mice, which is an unprecedented approach in the field [1].

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