低氧/厌氧产品案例——低氧与肝癌耐药研究

文章题目：Vandetanib-eluting radiopaque beads for chemoembolization: physicochemical evaluation and biological activity of vandetanib in hypoxia

万德他尼洗脱不透射线珠用于化疗栓塞:缺氧时万德他尼的理化评价和生物活性

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工作站使用情况：Invivo2

使用气体浓度：低氧（1% O_2）

摘要：万德他尼洗脱不透射线珠(VERB)已被开发用于肝肿瘤的经动脉化疗栓塞，其目标是将栓塞与抗血管生成治疗的局部递送相结合。本文主要研究在肝细胞癌(HCC)的治疗中，栓塞诱导的缺氧如何影响血管内皮生长因子受体(VEGFR)和表皮生长因子受体(EGFR)抑制剂万德他尼（vandetanib）的抗肿瘤活性。我们研究了万德他尼缺氧条件下对 HCC 细胞增殖、细胞周期和凋亡的影响，以及珠子对 3D HCC 球体的直接影响。万德他尼在体外抑制 HCC 细胞的增殖并诱导其凋亡，在低氧和常氧条件下效果相当。万德他尼抑制 ERK1/2 磷酸化并上调促凋亡蛋白 Bim 的表达，但这似乎不是万德他尼诱导所有细胞系中细胞死亡所必需的。Vandetanib 还抑制缺氧诱导的 HCC 细胞分泌 VEGF 抑制内皮细胞的增殖。用 VERB 孵育肿瘤球状体导致持续的生长抑制，相当于游离药物的效果。本研究表明结，即使在缺氧条件下，vandetanib 对 HCC 细胞也具有抗血管生成和直接抗癌活性，这证明了作为新型抗癌剂的 VERB 的进一步评价。

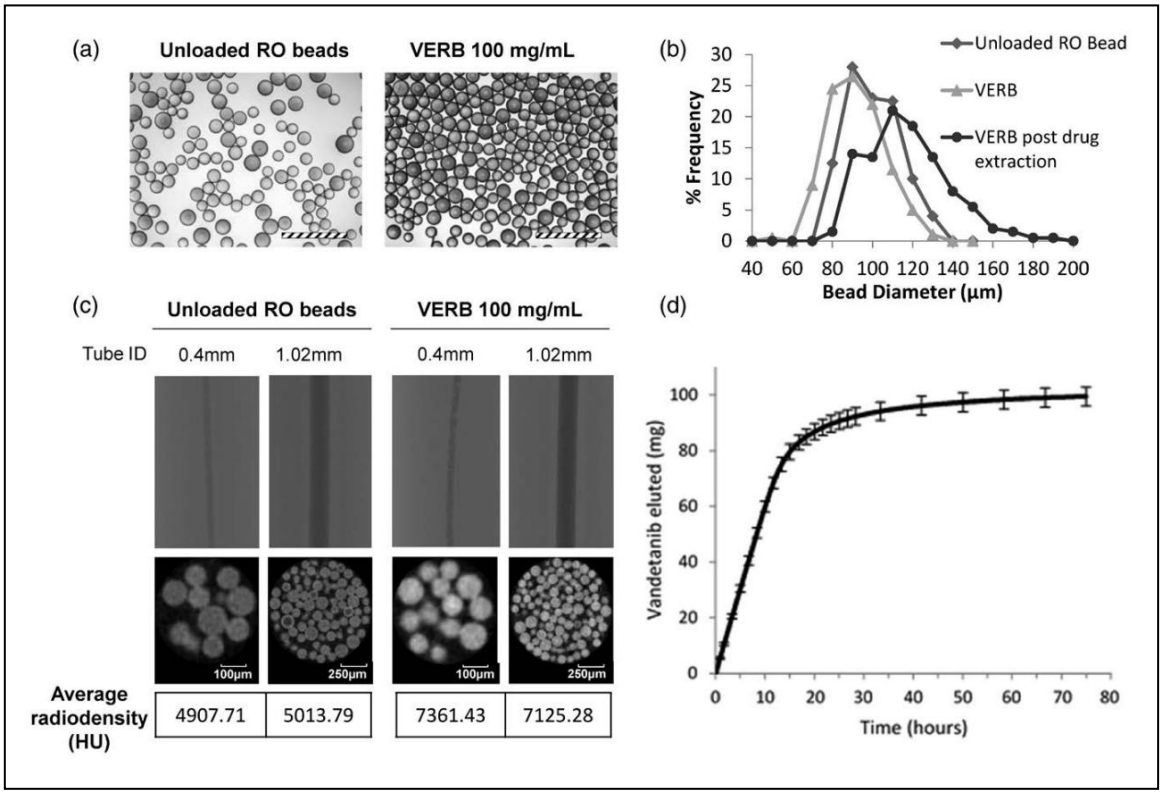

Figure 1.Physicochemical characterisation of vandetanib-eluting radiopaque beads (VERB). (a) Optical micrographs of unloaded radiopaque beads (left) and beads that have been loaded with 100 mg/ml vandetanib, lyophilised, gamma sterilised and rehydrated (right). Scale bars 500 µm. (b) Relative abundance histograms showing the distribution of beads by diameter during different stages of the drug loading process: preloading, loaded, sterilised and rehydrated, and postelution beads. n = 200 beads sized per sample. (c) X-ray shadowgraphs of beads in line phantoms of known diameter, and µ-CT cross sections of each tube. The average radiodensity of the cross section is reported below in Hounsfield units (HU). (d) Vandetanib released from 1 ml of VERB in an in vitro open loop flow through column elution model, mean ± SD of three independent experiments..

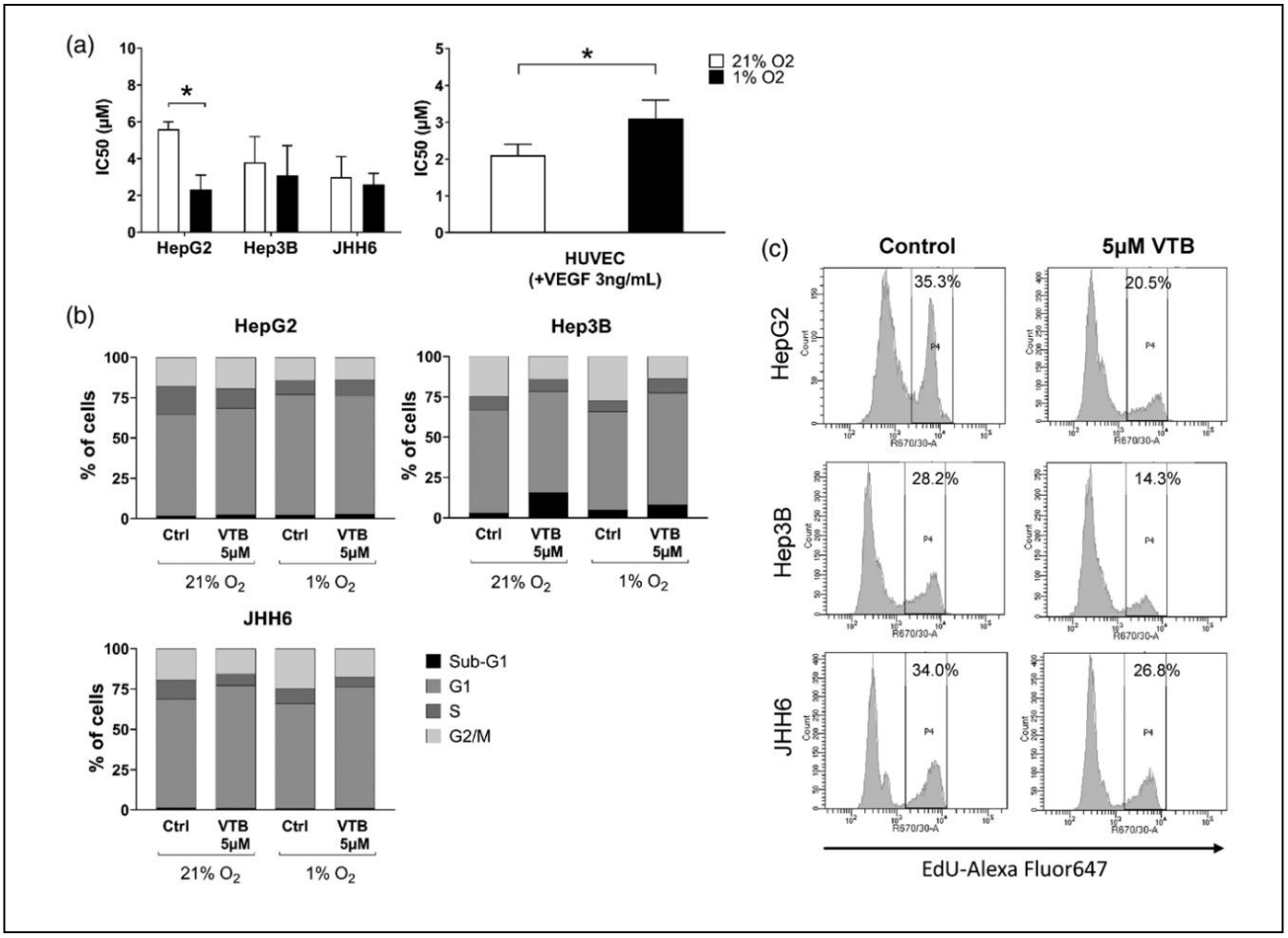

Figure 2.effects of vandetanib on cell cycle and proliferation. (a) Vandetanib IC50 in normoxia (21% O2) or hypoxia (1% O2) determined using the WST-1 assay in HCC cells (72 h incubation), or HUVEC (24 h incubation in the presence of VEGF). n = 3, error bars denote 95% confidence interval. *IC50 significantly different (extra sum-of-squares F test). (b) Effect of 24 h incubation with vandetanib (5 μM) in normoxia (21% O2,) or hypoxia (1% O2) on cell cycle distribution of HCC cells (mean % of total population, n = 3). (c) Flow cytometry analysis of cell proliferation by EdU uptake after 24 h treatment with 5 μM vandetanib in normoxia, plots representative of three independent experiments. EdU, 5-ethynyl-2′-deoxyuridine; HCC, hepatocellular carcinoma; HUVEC, human umbilical vein endothelial cell; VEGF, vascular endothelial growth factor.

万德他尼（vandetanib）的理化特性（图 1）；

在缺氧条件下，肝癌细胞 HepG2 细胞对凡德他尼的敏感性显著高于常氧，而肝癌细胞 Hep3B 和 jh6 在易感性上没有差异（图 2a）；

用万德他尼处理 24 小时导致 HCC 细胞的细胞周期分布的轻微变化，这在细胞系之间是不同的(图 2b)；jh6 的 G1 期细胞比例的增加表明细胞周期停滞，而 Hep3B 细胞的亚 G1 部分 vandetanib 治疗后增加，表明细胞凋亡。当用 vandetanib 处理时，通过促增殖(EdU 标记)细胞的减少证实了 G1 阻滞(图 2c)；缺氧本身并没有显著改变 Hep3B 或 jh6 细胞中的细胞周期分布，而未经处理的低氧 HepG2 细胞的增殖指数(S 期%)与常氧对照组相比降低，这可能有助于肝癌细胞在低氧中对 vandetanib 的敏感性增加。