

中文摘要

近年來斑馬魚生物模型被廣泛地應用於癌症研究。其中，斑馬魚異種腫瘤移植模型具有多項獨特優點，包含：斑馬魚飼養維護設備價格便宜、容易操作、可降低實驗藥物的使用量、在基因體學/蛋白質體學研究上有多種工具與方法可以搭配應用，如斑馬魚胚胎原位雜合技術以及免疫螢光染色技術等。不同於其他常見的模式生物，斑馬魚胚胎具有高度透明性，此優點對於在活體上觀測癌症發展以及癌症誘發之血管新生研究有莫大的助益。因此我們利用此模型來研究癌症誘發之血管新生。

卵巢癌近年來為婦科癌症死亡率較高的癌症之一。其惡性程度與腫瘤誘發之血管新生有密切的關係。近年來有報導指出，惡性腫瘤以及其誘發之血管新生與其周遭之 M2 表現型之腫瘤相關巨噬細胞有高度相關性，然而對於腫瘤以及腫瘤相關巨噬細胞之交互作用機制目前仍待釐清。

本篇研究中，我建立了斑馬魚腫瘤異種移植模型，並結合活體外實驗，釐清在腫瘤微環境中惡性腫瘤誘發血管新生的分子機制。在活體外實驗中，我們發現卵巢癌細胞 (SKOV3 cells) 之血管新生因子 (VEGFA) 以及人類組織蛋白酶 S (cathepsin S) 之表現量會在其與 M2 極化之巨噬細胞共同培養後大量上升。而在斑馬魚異種腫瘤移植模型上，我們發現當 M2 極化之巨噬細胞與卵巢癌細胞被共同移植時，腫瘤誘發之血管新生現象會顯著提升。我們的結果顯示腫瘤相關巨噬細胞主要是藉由提升卵巢癌細胞之血管新生相關基因表現，促進腫瘤誘發之血管新生。

Abstract

Zebrafish model have become a powerful tool in cancer research in recent years. The advantages of the zebrafish tumor xenograft model include: low cost, easy experimentation, reduced dosage for drug test, feasibility of various genetics/proteomics approaches such as whole mount in situ hybridization and whole mount immunocytochemistry. Different from other vertebrate organisms, the transparency of zebrafish embryo allowed us to monitor tumor progression and the tumor-induced angiogenesis in live embryos. In addition, zebrafish tumor xenograft model is much more rapid and cheaper than the current mouse model. Thus, here I aimed to use this model in tumor-induced angiogenesis research.

Ovarian carcinoma is considered as one of the leading gynecologic cancers with high mortality rate. The tumor malignancy is highly associated with tumor-induced angiogenesis. The tumor-associated macrophages (TAMs) with M2-like phenotype have been reported with tumor malignancy by promoting tumor-induced angiogenesis; however, the mechanisms of the interaction between cancer cells and macrophages are incompletely understood.

In this study, I established the zebrafish tumor xenograft model to accompany the *in vitro* cell-based assays to elucidate the molecular mechanism of tumor-induced angiogenesis in the cancer microenvironment. I have identified that the VEGFA and cathepsin S are induced in SKOV3 cells after co-cultured with M2-polarized macrophages. Furthermore, the zebrafish tumor xenograft model indicated when co-injected with M2-polarized macrophages, the tumor-induced angiogenesis was significantly increased. In conclusion, my results revealed that the tumor-associated macrophages could trigger the ovarian cancer cells to up-regulate angiogenesis-related genes in promoting tumor-induced angiogenesis.