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Autophagy induced by 5-fluorouracil and hypoxia in CD133+ colon carcinoma cells maintain the cytoactive

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Objective: Autophagy play a different role in tumer cell death and survival, the effection of autophagy in $CD133^+$ stem cell like caner cells is still unclear. The purpose of this study was to investigate the change and effection of autophagy induced by chemotherapeutics and hypoxia in $CD133^+$ colon carcinoma cells.

Methods: The $CD133^+$ subpopulation of colon carcinoma cell line SW480 was purified with MACS(magnetic activated cell-sorting system), and enriched by serum-free medium under floating culture system. The hypoxia microenvironment with 1% oxygen concentration was established using the anaerobic jar. The $CD133^+$ cells were incubated in hypoxia microenvironment or with 1μg/mL 5-fluorouracil(5-FU) for 24 hours to 48 hours. And then the viability of cells, autophagy and autophagy related proteins were detected. Furthermore, the immunohistochemical staining in 94 cases of colorectal cancer tissue was performed to anlysis the relationship between the classification, metastasis, Duke's staging and the expression of HIF-2α and Beclin 1.

Results: The emergence of a large number of autophagsomes was observed by transmission election microscope following 5-FU treatment in $CD133^+$ cells, the number of MDC positive utophagy vesica increased too, and the fluorescence intensity of MDC was significantly increased using FCM assay($P<0.05$). In that process, the transformation of autophagy related protein LC3-I to LC3-II enhanced, the expression of LC3-II significantly increased, but the transformation decreased following addition of 3-MA for 48 hours, the level of LC3-II reduced, but was still higher in comparison with 5-FU treated cells ($P<0.05$). Simultaneously, the viability and cloning efficiency decreased after addition of 3-MA ($P<0.05$). In a similar vein, the number of utophagy vesica and fluorescence intensity of MDC significantly increased after exposing $CD133^+$ colon carcinoma cells to hypoxia ($P<0.05$), and the expression of LC3-II significantly increased, but the viability of cells didn't decline. Immunohistochemical datas demonstrated that both of HIF-2α and Beclin 1 had a positive relationship with classification and Duke's staging in colorectal cancer ($P<0.05$), and the metastasis of lymphnode was positively correlative with Beclin 1 and negatively with HIF-2α ($P<0.05$).

Conclusion: Our datas indicated that 5-FU and hypoxia microenvironment could induce the enhancement of autophagy and maintain cell viability in $CD133^+$ cancer cells, The autophagy perhaps participate in the resistance to the damage of hypoxia and chemotherapeutics in $CD133^+$ cancer stem cell like cells, and promote the survival and metastasis of cancer.

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