Cytochrome C Oxidase Activity and Chemoresistance

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Most cultured glioma cells die under temozolomide (TMZ) treatment. However, a U251 glioma strain that proliferates under 500uM TMZ, termed "UTMZ", has been derived from U251 cells by resistance selection to increasing TMZ concentrations. The TMZ-dependent acquired chemoresistance is due to a mitochondrial adaptive response to TMZ genotoxic stress with a major contribution from cytochrome c oxidase (CcO). Elevated CcO activity in UTMZ cells was found to be associated with an isoform switch in the regulatory subunit COX4. Parental U251 cells express COX4-2 isoform, while UTMZ cells were found to express COX4-1 isoform. It was hypothesized that subunit COX4-1 is associated with enhanced CcO activity and chemoresistance. U251 cells overexpressing COX4-1 subunit were successfully obtained. The overexpressed COX4-1 protein was detected by Western blot in mitochondrial fractions of these clones. Increased CcO activity was found in all the clones overexpressing COX4-1 protein. CcO activity increased in these clones, and COX4-1 overexpressing clones showed resistance to TMZ. In contrast, wild-type U251 cells died after 72hr exposure to 500uM TMZ. These results support the view that COX4-1 and the level of CcO activity play an important role in TMZ-resistance, which suggested the switch in COX4 subunit provides a mechanism to maintain the efficiency of respiration under conditions of reduced O2 availability. It was concluded that expression of COX4-2 provides U251 cells with a mechanism to switch from oxidative phosphorylation to an anaerobic ATP production. However, expression of COX4-1 in UTMZ may permit the allosteric inhibition of CcO by ATP, adjusting energy production to match cellular energy requirements in the cancer cell.

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