DIFFERENTIAL EXPRESSION OF E-NTPDASES MODULATES GLIOMA GROWTH

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Extracellular ATP modulates a variety of biological effects, including cell death and cell proliferation. Such actions are mediated by purinergic receptors and controlled by ecto-nucleoside triphosphate diphosphohydrolases (E-NTPDases), a family of ecto-enzymes that hydrolyze extracellular nucleotides. Studies from our group have shown that alterations in the purinergic signaling could be involved in glioma progression, the most common and devastating primary brain tumor. Glioma cells have a low expression of all E-NTPDases, particularly NTPDase2, when compared to astrocytes. We have previously shown in an *in vivo* rat glioma model that the co-injection of apyrase, an enzyme that hydrolyzes equally well ATP and ADP, significantly decreases the tumor size, the mitotic index and the malignance of implanted tumor. Here we show that NTPDase2/CD39L1 overexpression, an enzyme that hydrolyzes preferentially ATP, dramatically increases the glioma growth and malignancy characteristics. Additionally, C6-YN2 derived gliomas exhibited massive presence of platelets in the tumor area, with increased CD31/PECAM-1, VEGF and OX-42 immunostaining. Treatment with clopidogrel, an antagonist of P2Y12, reduced the tumor growth, the P-selectin, CD31/PECAM-1, VEGF and OX-42 immunostaining. These data suggest that the ADP produced by NTPDase2 activity stimulates platelets migration to the tumor site, which probably play an important role on tumor progression by targeting angiogenesis and by regulating the inflammatory response. In conclusion, our findings reinforce the important role performed by the different E-NTPDase members that, by working in a highly organized enzymatic chain, maintain the extracellular nucleotide equilibrium and control the effects mediated by purinergic receptors.
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