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7-Nitro-2,1,3-benzoxadiazoles, a promising strategy for drug-resistant tumors

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A well-established approach for fighting cancer is based on signal-transduction inhibitors directed towards protein kinases involved in tumor development,and oftenused in combination with chemotherapy. However, several chemotherapeutic agents require the activation of the c-Jun N-terminal kinase (JNK) and p38 MAP-kinases to cause tumor cell death; therefore, activation of this pathway may enhance the anti-proliferative and pro-apoptotic effects of these drugs. The glutathione transferase GSTP1-1, an enzyme present at high levels in many solid tumors and overexpressed in drug-resistant ones, is a natural JNK inhibitor. The protein–protein interaction involving GSTP1-1 and JNK is an important mechanism for suppressing the response to apoptotic stimuli in tumors. In this regard, we have obtained biochemical evidence for direct interaction between GSTP1-1 and TNF receptor-associated factor 2 (TRAF2) as well, TRAF2 being an upstream adaptor protein responsible for the activation of JNK and p38. The TRAF2-GSTP1-1 complex is constitutively present in different tumor types, but can be disrupted by the strong GSTP1-1 inhibitor 6-(7-nitro-2,1,3-benzoxadiazol-4-ylthio)hexanol (NBDHEX); this results in JNK phospho-activation and tumor cell death. Therefore, agents directed towards GSTP1-1 and able to activate at different levels the MAPK/JNK signaling cascade may represent an alternative strategy for fighting cancer. We have synthesized several NBDHEX derivatives, endowed with higher solubility in water, with excellent tolerability and with antitumor activity against poorly responsive tumors. These compounds are very effective *in vivo* against human melanoma models resistant to vemurafenibor to temozolomide. These findings support the potential use of these novel compounds as part of the new therapies for cancer treatment as single agents or in combination regimens.

Biography

Anna Maria Caccuri graduated with Honors with a degree in Biological Sciences from the University of Rome “Sapienza”. She is Associate Professor of Biochemistry at the Department of Experimental Medicine and Surgery of the University of Rome “Tor Vergata”. She has published 75 papers in reputed peer reviewed journals.

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