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HuR and doxorubicin: How an RNA binding protein is involved in drug resistance

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HuR, an RNA binding protein involved in the post-transcriptional regulation of a wide spectrum of mRNAs, has been demonstrated to be a determinant of carcinogenesis and tumor aggressiveness in several cancer types. In this study, we investigated the role of HuR in the apoptosis and in the chemoresistance induced by the widely used anticancer drug doxorubicin in human breast cancer cells (MCF-7). We challenged a small library of about 80 chemical compounds with an high content screening assay to quantitavely measure HuR translocation. We showed that HuR acts in the early phase of cell response to doxorubicin, being induced to translocate into the cytoplasm upon phosphorylation. Reducing HuR levels diminished the apoptotic response to doxorubicin. We identified a number of compounds that can inhibit HuR cytoplasmic accumulation and pointed to PKA, Rho kinase and PKCδ as potential HuR regulators. Among the hits rottlerin showed to be the most effective in blocking HuR nuclear export and in having correspondingly antagonistic effects with doxorubicin on cell toxicity. Co-immunoprecipitation of PKCδ and HuR upon doxorubicin confirmed the validity of HCS indications. In in vitro selected doxorubicin resistant MCF-7 cells (MCF-7/doxoR) overexpressing the multidrug resistance (MDR) related ABCG2 transporter, we observed a significant HuR downregulation that was paralleled by a corresponding downregulation of HuR targets as TOP2A and by loss of rottlerin toxicity. Restoration of HuR expression in these cells resensitized MCF-7/doxoR cells to doxorubicin, reactivating the apoptotic response. The present study shows that HuR is necessary to elicit the apoptotic cell response to doxorubicin, that restoration of HuR expression in resistant cells resensitizes them to the action of this drug. Moreover we suggest a novel mechanism of pharmacoresistance based on the interplay among the doxorubicin target TOP2A, its post-transcriptionally regulator HuR and the signaling control of PKCδ.

Biography

Alessandro Provenzani got his PhD in chemistry in 2003 at Centre for Magnetic Resonance (CERM, University of Florence) and then he worked for the Pharmacogenomic Foundation (FiorGen) as research scientist. In 2006 he moved, as post-doc, at the University of Trento where he became Assistant Professor in Applied Biology in 2009. He received a start-up grant to lead his own laboratory (Laboratory of Genomic Screening) and has won competitive grants, as responsible of unit research, in different project proposals at the Ministery of Health of Italy (Young Researcher Program) and during the FP7 European Research Funding Program (PANACREAS).

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