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Visceral leishmaniasis in Benishangul-Gumuz Regional State, Western Ethiopia: Reemerging or emerging?

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Kala-azar is a growing public health problem in Ethiopia. Benishangul-Gumuz Regional State was previously not known to be endemic for the disease. In response to a case report from the region, we conducted a rapid assessment survey. A pretested questionnaire was used to capture sociodemographic and clinical histories pertinent to kala-azar. Study participants with complaints of fever and headache for 2 weeks or more were tested for kala-azar and malaria. All participants were screened with the leishmanin skin test and the direct agglutination test for exposure to *Leishmania*, defined as a positive result with either or both tests. Of 275 participants, 20 were exposed giving an overall leishmaniasis seroprevalence rate of 7.3%. Among the 20 positive individuals, 19 were farmers and nine of them reported no travel history outside their district. It appears that kala-azar is emerging in Dangur and Guba districts of Benishangul-Gumuz Regional State, probably in connection with human encroachment into one or several previously out-of-reach zoonotic foci. We recommend integrated epidemiological surveys for confirmation and early containment of disease transmission in the area.

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Inhibiting MADD phosphorylation increases TRAIL sensitivity of anaplastic thyroid cancer cells by activating both intrinsic and extrinsic apoptotic pathways

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Thyroid cancer is the most frequently occurring endocrine cancer. Anaplastic thyroid cancer (ATC) shows very poor prognosis (mean survival <6 months) and have limited treatment options. TNF-related apoptosis-inducing ligand (TRAIL) can induce tumor cell specific apoptosis in multiple cancers without affecting non-tumor cells. We have previously demonstrated that Map kinase Activating Death Domain containing protein (MADD), is a cancer cell survival factor, its knockdown leads to cancer cell apoptosis and Akt-mediated MADD phosphorylation confers resistance to TRAIL induced apoptosis in thyroid cancer. Therefore, we hypothesized that ATC TRAIL sensitivity could be enhanced by preventing MADD phosphorylation. MADD expression and TRAIL resistance was determined by Western blotting and active caspase 3 staining in several ATC cell lines harboring mutations in cancer driver genes including BRAF, Akt and PTEN. MADD phosphorylation was inhibited by site directed mutagenesis of Akt phosphorylation sites and exogenously expressing the mutant constructs to determine the effect on TRAIL induced apoptosis. MADD was overexpressed in all ATC cells compared to the normal thyroid tissues irrespective of the underlying genetic mutation and/or inherent TRAIL resistance. Further, preventing MADD phosphorylation by site directed mutagenesis in ATC lines resulted in significantly increased TRAIL-induced apoptosis accompanied by the activation of both intrinsic and extrinsic apoptotic pathways. Additionally, we inhibited endogenous MADD phosphorylation by using AKT inhibitors. PI3-kinase inhibitor which acts upstream of AKT and MADD in combination with TRAIL showed increased apoptosis in ATC cell lines in comparison to TRAIL or PI3K inhibitor alone. Thus, we conclude that prevention of MADD phosphorylation by site directed mutagenesis or PI3K inhibitors improves TRAIL susceptibility of ATC cells. Further studies are warranted to delineate the underlying mechanism of action and determine the clinical utility of this approach to treat ATC.

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