Lunch Talk

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Dimethyl fumarate inhibits tumor growth and metastasis formation in NF-kB dependent tumors

by Karsten Gülow

About Karsten Gülow

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- **2018 - present**: Head of Research at the Clinic and Polyclinic for Internal Medicine I, Director Prof. Dr. Martina Müller-Schilling at the University Hospital Regensburg (UKR).
- **2011 - 2018**: Deputy Head of Department, Head of the working group "The role of oxidative signaling in Activation Induced Cell Death and AIDS" in the department of Prof. Dr. Peter H. Krammer, German Cancer Research Center (DKFZ), Immunogenetics (D30).
- **2004 - 2011**: Head of the working group "The role of oxidative signaling in Activation Induced Cell Death and AIDS" in the department of Prof. Dr. Peter H. Krammer, German Cancer Research Center (DKFZ), Immunogenetics (D030).
- **2002 - 2004**: Research associate in the laboratory of Prof. Peter H. Krammer, German Cancer Research Center (DKFZ), Immunogenetics (D030).
- **1998 - 2001**: Scientific employee at the Biochemistry Center (BZH) of the Ruprecht-Karl University, Heidelberg; Director Prof. Dr. Felix Wieland, Group Leader Prof. Dr. Ingrid G Haas.

Abstract

Despite intensive efforts in recent years, a curative therapy for cutaneous T-cell lymphoma (CTCL) has not yet been developed. Therefore, the establishment of new therapeutic approaches with higher efficacy rates and milder side effects is urgently needed. A characteristic feature of the malignant T-cell population in CTCL is resistance to cell death resulting from constitutive NF-κB activation. Constitutively active NFκB promotes tumor survival by inducing anti-apoptotic proteins such as apoptosis inhibitors (IAPs) and FLICE-like inhibitory proteins (cFLIPs). The small molecule DMF inhibits thioredoxin-1 (Trx1), an important regulator of NFκB transcriptional activity. DMF-mediated inhibition of NFκB enables ripoptosome formation by down-regulating IAPs and cFLIPs. DMF thus induced cell death by means of the ripoptosome in primary patient-derived CD4(+) cells but hardly in T cells from healthy donors. To investigate the effects of DMF in vivo, we developed two CTCL xenograft mouse models with different localization of the T-cell infiltrate in the skin. Treatment with DMF delayed the growth of CTCL tumors and prevented the formation of distant metastases. In addition, DMF resulted in increased cell death in primary CTCL tumors and in liver metastases. In conclusion, DMF treatment is an interesting therapeutic option in CTCL because it restores apoptosis of CTCL *in vitro* and in preclinical *in vivo* models.