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HTLV-I inhibits stress granules formation by interacting with the histone deacetylase 6 (HDAC6)

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Human T cell leukaemia virus type-1 (HTLV-1), the first pathogenic retrovirus discovered in humans 29 years ago is the causative agent of two major diseases: a rapidly fatal leukaemia designated adult T-cell leukaemia (ATL) and a neurological degenerative disease known as tropical spastic paraparesis (TSP) or HTLV-1 associated myelopathy (HAM). Approximately 5% of HTLV-1-infected individuals develop malignancy after 40 to 50 years of latency. The viral transcriptional activator and oncoprotein Tax-1 has been the major focus of scientific investigation because of its numerous and crucial roles in the pathogenesis of HTLV-1-induced diseases.

One of the most immediate responses to cellular stress such as viral infection, oxidative stress or UV, is a reversible block of mRNA translation. To achieve this, the cell sequesters mRNA in specific cytoplasmic structures called stress granules. Because mRNA coding for stress responsive proteins are not sequestered in stress granules, this mechanism allows the cell to focus on responding adequately to the stress stimulus. Stress granules are characterized by the presence of specific proteins, G3BP, Tiar and Tia-1. Recently, the class II histone deacetylase HDAC6 was identified as a critical component of stress granules. Indeed, deletion of HDAC6 impairs formation of stress granules.

It is well known that Tax-1 accumulates in the cytoplasm under stress [1]. We have observed that in stressed cells, cytoplasmic Tax-1 concentrates into 'Tax-1 cytoplasmic structures' that we identified as stress granules. Indeed, upon stress, Tax-1 colocalizes with G3BP and Tiar, two specific markers for stress granules. Moreover, we have shown that Tax-1 is able to inhibit stress granule formation. By screening various stress granules components, we have unravelled a specific interaction between Tax-1 and HDAC6. Deletions analysis demonstrated that the interaction is mediated by the ubiquitin binding domain of HDAC6 and the zinc finger region of Tax-1. Interestingly, a Tax-1 mutant deficient for binding to HDAC6 still localizes to stress granules upon stress but proves unable to inhibit stress granule formation.

Our results thus demonstrate that Tax-1 impairs stress granules formation by interfering with one of their key components. By preventing stress granules formation, Tax could prevent adequate management of the stress by the infected cell, which could participate in cellular transformation processes. Our findings thus unravel a new strategy developed by HTLV-1 and we postulate that this new function of Tax might have important role in HTLV-I-induced transformation and oncogenesis.

References

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