TUMOR GROWTH ARREST: INVOLVEMENT OF THE MUTATION IN THE CATARITIC REGION OF JAK1

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ABSTRACT

Interferon-γ is cytokine that has antiviral, antiproliferative and immunomodulatory effects. Since the original discovery of the classical JAK-STAT1 signaling pathway, it has become clear that the coordination and cooperation of multiple distinct signaling cascades are required for the generation of responses to IFN-γ. The receptor-associated JAK1 and JAK2 activities are important for interferon-γ response. In many cases, the lack of antigen presentation can be attributed to the down regulation of genes needed for antigen processing, such as the TAP1 and LMP2, which are greatly induced by IFN-γ signalling. The G871E mutation in ATP-binding region of JAK1 has already been identified in uterine leiomyosarcoma (Ut-LMS) cells, and possibly attribute to loss of IFN-γ inducible TAP1 and LMP2 expression. However, the effect of mutant JAK1 on sarcomagenesis and malignancy has not been fully understood. Here, the differential responsiveness to IFN-γ of the cells, which have exogenous mutant JAK1-G871E activity, was investigated. We now show the defective tyrosine kinase activity of mutant JAK1-G871E, suggesting the loss of IFN-γ inducible TAP1 and LMP2 expression. Importantly, it is likely that G871E mutation of JAK1 results in defective IFN-γ induced cell growth arrest due to loss of LMP2 expression. Understanding the mechanisms by which sarcoma cells circumvent cytokine signaling, thereby JAK1 mutation, rather than evading antitumor-specific immunity, markedly affects the cell proliferation.

Keywords: LMP2, JAK1, IFN-γ, Leiomyosarcoma, Growth arrest.