Annals of Oncology 29 (Supplement 6): vi18–vi20, 2018
doi:10.1093/annonc/mdy315

PERSONALISED MEDICINE APPLIED TO IMMUNOTHERAPEUTICS

52P Hedgehog pathway influence in the immune escape of tumor cells through PDL-1 modulation

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Background: In recent years, immunotherapy has shown remarkable success in the treatment of several cancers. Masking PDL-1 on cancer cellular surface or PD1 on T-cells may increase the lymphocyte activity against the tumor. Intracellular regulation of PDL-1 may thus be a promising therapeutic strategy. However, the mechanism regulating PDL-1 expression remains unclear. Moreover, there are evidences supporting the idea that deregulation of Hedgehog (Hh) signalling has a role in immunity and inflammation. Therefore, we investigated whether activation of the Hh signalling contributes to regulate PDL-1 or PD1 expression and whether its pharmacological modulation affects the anti-tumor function of activated lymphocytes.

Methods: We used a panel of human pancreatic and breast cancer cell lines, with different ER, PR and HER2 expression patterns. The effects induced by Hh inhibition, through the Smo-inhibitor NVP-LDE225, on signal transduction in cancer cells were investigated. We also tested how the overexpression of GLI1, tGLI1 and GLI3, main transcription factors in the Hh pathway, could affect the expression of PDL1.

Results: Hh inhibition reduced the expression of PDL1 in all analysed cell lines. This effect is counteracted by upregulation of PDL-1, when GLI1 and, even more, tGLI1 are overexpressed. NVP-LDE225 treatment modulates the production of several secreted factors, such as secreted IL6-receptor which acts as an anti-inflammatory molecule.

Conclusions: Our results suggest that Hh pathway has a specific role in cancer immune evasion trough PDL-1 modulation. The inhibition of the Hh pathway could represent an interesting therapeutic approach in combination with anti-PD1 drugs.

Legal entity responsible for the study: Prof. Roberto Bianco.

Funding: Has not received any funding.

Disclosure: All authors have declared no conflicts of interest.