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Modulo per la sottomissione abstract ricerca di LABORATORIO

Titolo (massimo **15 parole**)

The ETS inhibitors YK-4-279 and TK-216 interfere with SPIB and synergize with lenalidomide in DLBCLs

Autori (cognome e iniziali, es: Grassi L.)

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Testo (massimo **250 parole**, preferibilmente in italiano (accettato anche in inglese), suddiviso in Introduzione, ***Metodi***, ***Risultati***, ***Conclusioni*** e ***Finanziamento***

Background. We have previously shown anti-lymphoma activity of YK-4-279, a small molecule inhibiting EWS1-FLI1/RHA binding in Ewing sarcoma, and its derivative TK-216, the first-in-class clinical inhibitor of ETS transcription factors. We present data on their mechanism of action.

Methods. Lymphoma cell lines were treated with single agents and combinations for 72h. RNA and proteins changes were analyzed as previously described.

Results. SPIB, among all the ETS-factors, presented the highest correlation with sensitivity to both compounds in the activated B cell diffuse large B-cell lymphoma subtype (ABC DLBCL) ($P<0.05$). In a combination screening on lymphoma cell lines, both molecules were synergistic with lenalidomide, a drug interfering with SPIB/IRF4 axis. We studied transcriptome of lymphoma cell lines exposed to YK-4-279, TK-216 or control. Both compounds affected SPIB and IRF4 target genes. To further assess the contribution of SPIB and IRF4 in the mechanism of action of YK-4-279 and TK-216, we treated lymphoma cell lines with the drugs and performed co-immunoprecipitation experiments. The binding of SPIB to RHA and DDX5 was decreased exposing the cells to YK-4-279 or TK-216 (500 nM, 4h). Moreover, similarly to lenalidomide, TK-216 decreased IRF4 and upregulated IRF7 protein levels.

Conclusions. In ABC DLBCL, pharmacological screening, transcriptome analysis and protein experiments indicate that YK-4-279 and TK-216 exert their anti-lymphoma activity via inhibition of the SPIB/IRF4 axis. A phase I study exploring TK-216 as single agent in lymphomas is expected to open in USA and Switzerland during 2018.

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Visto superiore (prego indicare Nome e Cognome del superiore)

Francesco Bertoni

Criteri per sottomissione Abstract:
NO Case report
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Invio Abstract