METHOD FOR ASSESSING THE EFFICACY OF IMMUNOMODULATORY DRUGS

Ref-Nr: TA-B74042

HINTERGRUND

Immunomodulatory drugs (IMiDs), such as thalidomide and its derivatives lenalidomide and pomalidomide, are key treatment modalities for hematologic malignancies like multiple myeloma (MM) and del(5q) myelodysplastic syndrome (MDS). Cereblon (CRBN), a substrate receptor of the CRL4 ubiquitin ligase complex, is the primary target by which IMiDs mediate anticancer and teratogenic effects. However, the physiological functions of CRBN are mostly unknown and the mechanisms by which IMiDs mediate their plethora of different antitumor and teratogenic effects have remained elusive.

LÖSUNG

This technology discovered the mechanism by which CRBN mediates ubiquitin-independent maturation and stabilization of the CD147–MCT1 complex, and demonstrates that IMiDs compete with CD147 and MCT1 for CRBN binding to exert versatile anti-tumor effects. CRBN mediates the folding and maturation of the CD147 and MCT1 proteins and thereby allows activation of the CD147-MCT1 transmembrane complex. The CD147-MCT1 complex is of vital importance for the regulation of cellular metabolism - particularly glycolysis, a major source of energy production in cancer cells. Notably, expression of CD147 and MCT1 is upregulated in multiple myeloma (MM), and both proteins have been critically implicated in the proliferation and survival of MM cells. All three established IMiDs (thalidomide, lenalidomide and pomalidomide) destabilize CD147 and MCT1, indicating the general drug-class-specific effect. The technology shows that destabilization of CD147 and MCT1 is predictive of a therapeutic response to IMiDs, and that this could be used as a biomarker. Moreover, given the location of the CD147–MCT1 complex at the cell surface and its functions, these proteins may represent accessible therapeutic targets in both IMiD-responsive and IMiD-resistant tumors.
Figure: A) IMiDs mediate their biological effects by destabilizing CD147 and MCT1. B) Destabilization of CD147 is predictive of a therapeutic response to IMiDs.

**VORTEILE**

- Using CD147/MCT1 destabilization as biomarker to:
  - reduce unnecessary treatment of IMiD-resistant patients and
  - reduce healthcare costs and drug-related toxicity
- Previously hard-to-treat patients could benefit from CD147/MCT1-targeting therapies
- Potentially extendable to other IMiD-sensitive or -resistant malignancies

**PUBLIKATIONEN & VERWEISE**