478 NLRC5 as a target to intervene MHC class 1 mediated immune responses

Asset Overview

Product Type	All the molecules (siRNA, peptides and others)
Indication	Cancer and other diseases
Current Stage	Lead optimization
Target(MoA)	Modulating MHC class I gene expression by controlling NLRC5
Brief Description	A method to modulate MHC class I gene expression by modulating NLRC5 expression and/or NLRC5 activity in a subject is provided. The method comprises administering to the subject a compound that modulates NLRC5 expression and/or NLRC5 activity in an amount effective to modulate MHC class I gene expression. Also described is a screen for compounds that modulate NLRC5 expression. Candidate compounds are tested for their ability to modulate NLRC5 expression.
Organization	Dana-Farber Cancer Institute

Differentiation

□ **A compound that modulates NLRC5 expression or activity inhibits/reduces MHC class I**

- Loss of MHC class I expression provides a key immune evasion strategy in many cancers, although the molecular mechanisms remain elusive
- MHC class I transactivator (CITA), known as "NLRC5" [NOD-like receptor (NLR) family, caspase recruitment (CARD) domain containing 5], has recently been identified as a critical transcriptional coactivator of MHC class I gene expression. In a screen for modifiers of the naive-primed transition, we uncover XMD series compounds, which selectively inhibit the Erk5 kinase

□ **NLRC5 is a novel biomarker and therapeutic target of cancer**

- In all the 21 tumor types we examined, NLRC5 expression was highly correlated with the expression of MHC class I, with cytotoxic T-cell markers, and with genes in the MHC class I antigen-presentation pathway, including LMP2/LMP7, TAP1, and β2-microglobulin.ERK5-overexpressing PC3 cells had significantly increased levels of proliferation, and invasion (emphasizing the relationship between ERK5 and the aggression of prostate cancer)
- Strikingly, NLRC5 expression was significantly associated with the activation of CD8+ cytotoxic T cells and patient survival in multiple cancer types. Thus, NLRC5 constitutes a novel prognostic biomarker and potential therapeutic target of cancers

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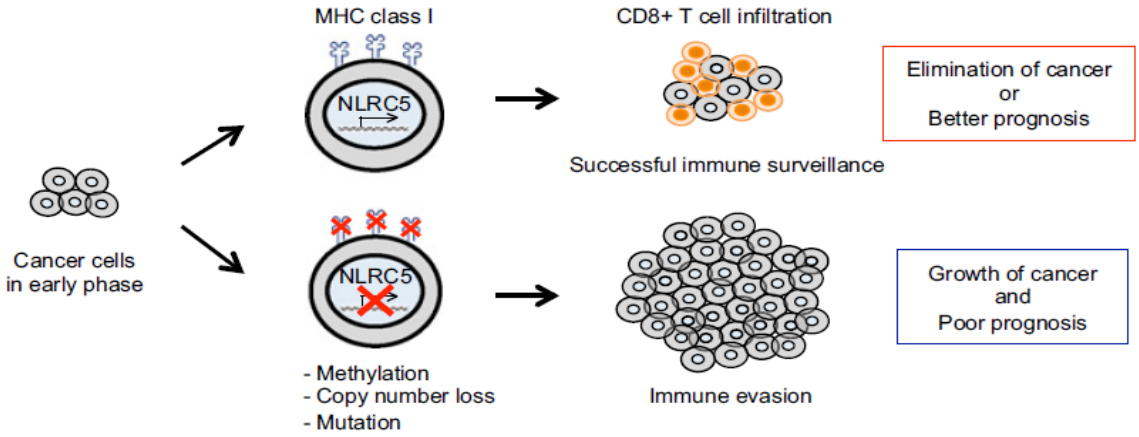
Key Data

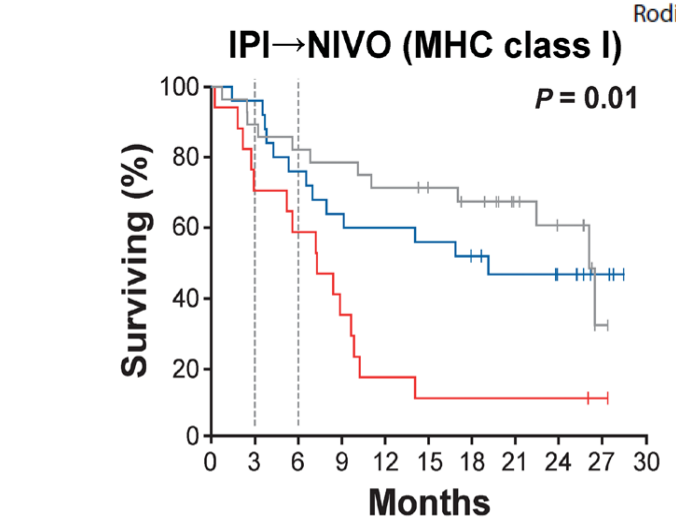
Model of cancer evolution targeting NLRC5 for immune evasion



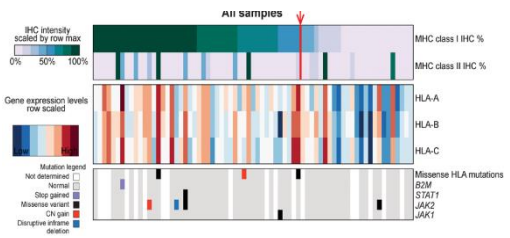
NLRC5-dependent MHC class I expression is crucial for CD8+ T-cell–mediated antitumor responses and the elimination of cancer cells. Genetic and epigenetic changes of NLRC5 occur during the evolution of cancer cells, leading to an impaired MHC class I system.

Summary of MHC class I data from the CheckMate 064 trial

Rodig *et al.*, *Sci. Transl. Med.* **10**, eaar3342 (2018) 18 July 2018



MHC class I	>50%	≤50%	Not evaluable/ missing
Median OS, months (95% CI)	19.1 (7.0, NR)	7.3 (2.7, 9.9)	26.1 (17.0, NR)
HR (95% CI)	0.38 (0.18, 0.82)		—



Heat map of tumor cells (0 to 100%) for MHC class I

Kaplan-Meier estimates of overall survival (OS) by MHC class I expression in baseline biopsy samples according to treatment arms. OS according to expression of MHC class I is divided according to the optimum (50%) for the IPI→NIVO arm.

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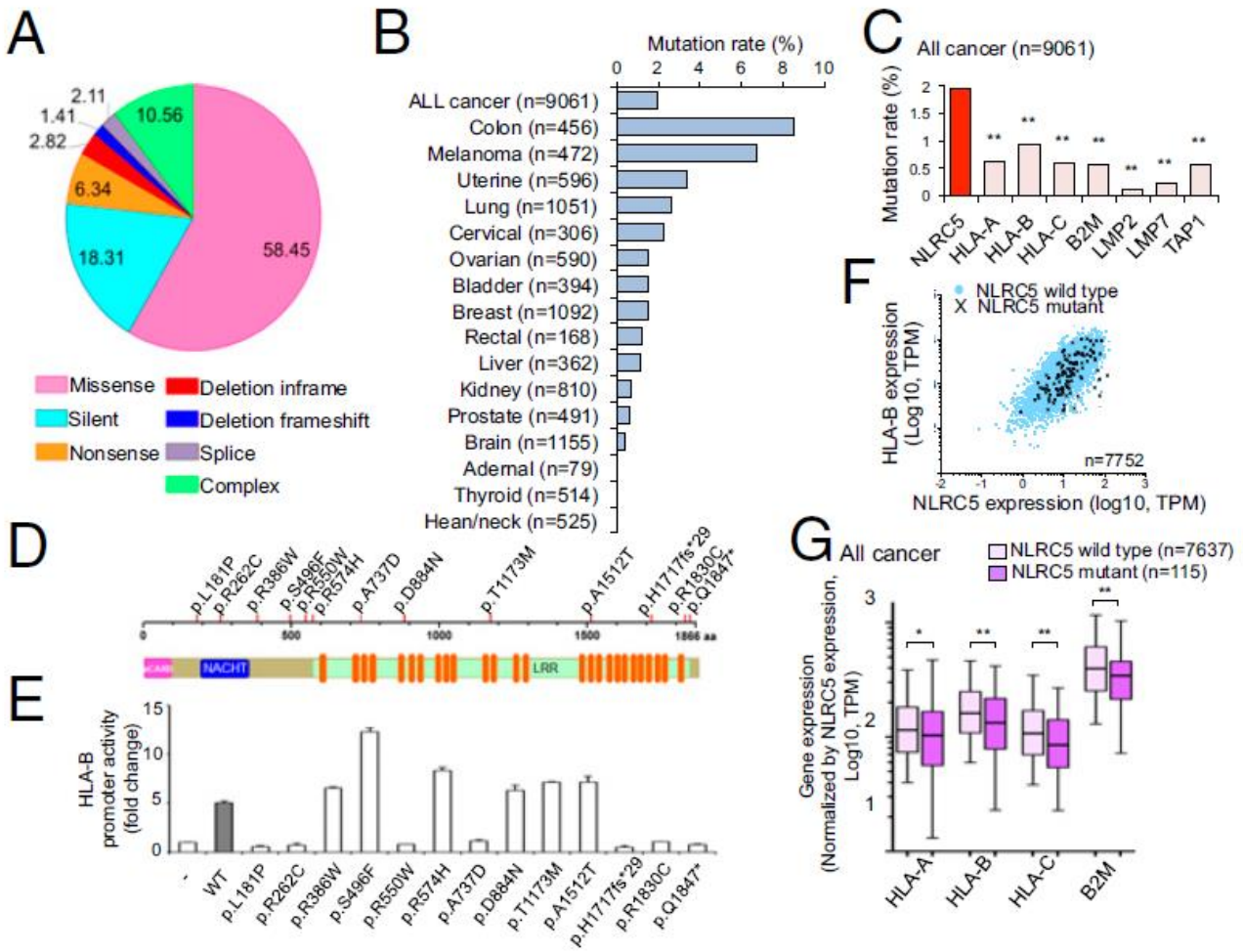
Somatic mutations in NLRC5 are correlated with reduced expression of MHC class I genes.



(A) Pie chart representing the percentage distribution of different types of mutations in NLRC5 in various cancer patients (n = 7,752). (B) Mutation rate in NLRC5 for 16 tumor types (n = 9,061). (C) Mutation rate in the indicated genes for 16 tumor types. Statistical significance was determined by the χ2 test (n = 9,061):. (D) Representation of NLRC5 indicating 13 mutations found in at least two different cancer patients. (E) HEK293T cells were cotransfected with either empty control vector or the respective NLRC5 mutant plasmid with HLA-B reporter plasmid, and HLA-B promoter activity was assessed by the dual-luciferase assay and normalized against Renilla firefly activity. (F) Scatter plots for the expression of NLRC5 and HLA-B for the NLRC5 wild-type group (blue circle) and the NLRC5 mutant group (black cross) in 16 tumor types (n = 7,752). (G) Box plots for the expression level of MHC class I-related genes normalized by the expression level of NLRC5 in 16 tumor types that are either NLRC5 wild type or NLRC5 mutant.

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Intellectual Property

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