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ABSTRACT PREVIEW: THE MYELOMA BIOMARKER GLUTAMINYL CYCLASE IS A NOVEL POST-TRANSLATIONAL MODIFIER OF IMMUNOGLOBULIN LIGHT CHAINS

The myeloma biomarker glutaminyl cyclase is a novel post-translational modifier of immunoglobulin light chains

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Introduction

There has been increasing interest in blood-based protein biomarkers that predict the future development of multiple myeloma (MM). Three groups have independently reported that higher levels of glutaminyl peptide cyclotransferase (QPCT) predict the development of MM. However, its function in plasma cell and myeloma biology are unknown. QPCT and its isoform QPCT-like (QPCTL) convert N-terminal glutamine (Q) and glutamate (E) to pyroglutamate (pE). Classically, this protects hypothalamic hormones from N-terminal peptidases, but it is also a drug target in amyloidogenic disorders like Alzheimer's. While N-terminal pE has been found on human antibodies for several decades, it is widely believed to be spontaneous and of no functional consequence. We now show that QPCT and or QPCTL actively modify light chain immunoglobulins in myeloma cell lines and that inhibition of this activity does not affect myeloma cell viability.

Methods

Immunoglobulin N-terminal amino acids from humans, mice and macaques were tabulated using data from the Observed Antibody Space. 4 MM cell lines and 3 non-MM blood cancer cell lines were treated with the QPCT inhibitor PBD150 and the dual QPCT and QPCTL inhibitor SEN177. Light chains were examined using isoelectric focussing at 24 hours and cell viability was assessed at 48 and 96 hours. Survival as a function of QPCT mRNA expression was assessed within the 977 patients of the COMMPASS cohort using the log-rank test.

Results

60% and 73% of heavy and lambda immunoglobulins begin with Q respectively. In comparison, < 1% of kappa light chains begin with Q but 30% begin with E. These features are evolutionarily conserved, being shared with C57BL/6 mice and Rhesus macaques. Isoelectric focussing revealed that treatment with SEN177, reduced the major light chain isoform in lambda secreting cell lines and resulted in the emergence of one new species in U266B1 and two new species RPMI-8226 and L-363. No changes were observed for JJN-3 kappa light chains, nor were changes observed when using the QPCT selective inhibitor PBD150. Despite higher levels of QPCT transcript being favourably prognostic for overall survival within the COMMPASS cohort (p=0.032), SEN177 and PBD150 had no impact on cell viability in any of the lines tested.

Conclusions

The strong conservation of N-terminal Q and E in immunoglobulin heavy and light chains suggests functional importance and show they are potential substrates for QPCT(L). We have shown that either QPCT, or more likely QPCTL, modify light chains and that in the absence of their activity, a second modification can occur. Ongoing work will measure light chain secretion via ELISA, characterise the new light chain isoforms with mass spectrometry, and confirm the isoform responsible following knock-down. It remains unclear whether QPCT actively drives MM progression and why higher baseline tumour expression of QPCT is favourably prognostic.

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