Universidad de Navarra

Máster en Investigación Biomédica
Facultad de Ciencias

Research Project Proposal
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Project Nº 2

Title: NMD as an endogenous mechanism to modulate tumour immunity

Department/ Laboratory Aptamer Laboratory, Department Molecular Therapy, Center for Applied Medical Research (CIMA).

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Summary:

The NMD process prevents the accumulation of mRNAs containing a premature termination codon (PTC). The recent clinical success of immune-checkpoint blocking antibodies in cancer patients has underscored the importance of the immune system in tumor control. However, just a small fraction of patients respond to the treatment. One of the possible reasons for the lack of effect in some cases is the lack of expression of potent tumor neoantigens ("foreignness") that could be recognized by the immune system. The source of tumor antigenicity comes from mutated genes that would codify for new proteins which therefore could be recognized by the immune systems as tumor neoantigens. An important fraction of these mutated genes would not even be translated from mRNA into proteins because NMD would degrade the mutated transcripts if they contain a PTC. Therefore, NMD would act in the tumor as a mechanism to hide tumor-specific antigens, limiting the real tumor antigenicity. The inhibition of NMD favors the expression of the repressed tumor antigens, in turn favoring the induction of tumor immunity (1,2). We have preliminary evidence that the levels of NMD expression could be intrinsically up-regulated by the tumor as mechanism of tumor antigenicity scape. The target inhibition of NMD by using aptamer technology (3) could be used to reverse this possible mechanism of immunoediting. The master student working on this project will be exposed to techniques of molecular biology to correlate the levels of NMD with tumor inflammation and they will participate in the development of aptamer-siRNA chimeras to target the inhibition of NMD.

References

1- Pastor F, et al. Induction of tumour immunity by targeted inhibition of nonsense-mediated mRNA decay. Nature. 2010

2- Soldevilla MM, et al. 2-fluoro-RNA oligonucleotide CD40 targeted aptamers for the control of B lymphoma and bone-marrow aplasia. Biomaterials. 2015.

3- Zhou J et al Aptamers as targeted therapeutics: current potential and challenges. Nature Reviews Drug Discovery. 2017.