

Epigenetic editing in the promoter of CXCL11 gene

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Extended Abstract

Introduction:

Statement of the Problem: Epigenetic engineering (editing) is an exciting path to novel therapeutics. Custom-designed demethylases allow gene-specific reactivation of epigenetically silenced genes. Progress in this area depends in great part on the choice of enzymatic effectors and their targeted binding to promoters. Here we report a successful use of a combination of TDG and Tet1 to enhance transcriptional responsiveness of CXCL11 gene in a murine fibroblast line. **Methodology & Theoretical Orientation:** We designed multiple fusion constructs (n=6) aimed to bind in relative vicinity of each other in the key regulatory areas of mCXCL11. Zinc-finger protein arrays served as DNA-binding domains; murine TDG isotype 2 and human Tet1CD were the enzymatic effectors. Constructs with catalytically inactive single aminoacid mutant enzymes served as controls. The constructs were delivered into 3T3 fibroblasts via lentiviral transduction. **Findings:** After 2 weeks of constitutive expression the pyrosequencing analysis demonstrated a decrease in CpG methylation by up to 40 percentage points in several loci in the targeted area. This was associated with a nearly 5-fold increase in transcriptional responsiveness of CXCL11 after stimulation with a combination of IFN γ and LPS. The maximum transcriptional responsiveness measured ~X 2000 times over baseline, vs. ~X 400 times in the control.

Conclusion:

We conclude that a combination of multiple TDG and Tet1 complexes with zinc-finger arrays is a promising approach in targeted demethylation and that CXCL11 is a rewarding target for future experimentation.

Recent Publications: 1. Gregory D J, Zhang Y, Kobzik L and Fedulov A V (2013) Specific transcriptional enhancement of inducible nitric oxide synthase by targeted promoter demethylation. *Epigenetics* 8(11):1205-12. 2. Gregory D J, Mikhaylova L and Fedulov A V (2012) Selective DNA demethylation by fusion of TDG with a sequencespecific DNA-binding domain. *Epigenetics* 7(4):344-9. 3. Gregory D J, Kobzik L, Zhang Y, McGuire C C and Fedulov A V (2017) Transgenerational transmission of asthma risk after exposure to environmental particles during pregnancy. *Am J Physiol Lung Cell Mol Physiol.* 313(2):L395-L405. 4. Mikhaylova L, Zhang Y, Kobzik L and Fedulov A V (2013) Link between epigenomic alterations and genome-wide aberrant transcriptional response to allergen in dendritic cells conveying maternal asthma risk. *PLoS One* 8(8):e70387. 5. Fedulov A V and Kobzik L (2011) Allergy risk is mediated by dendritic cells with congenital epigenetic changes. *Am J Respir Cell Mol Biol.* 44(3):285-92.

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