Project Title: Molecular basis for the epigenetic regulation of MGP in cancer

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Summary: (1000 characters)

Matrix Gla protein (MGP) was first identified as a physiological inhibitor of calcification[1] and the causal agent of the human Keutel syndrome, an autosomal recessive pathology associated to ectopical calcifications[2]. Lately, MGP was suggested to play a role in development, cell differentiation and tumorigenesis[3,4,5,6] but little is known about its transcriptional regulation with only two major regulators identified, retinoic acid[7] and FGF2[8]. DNA methylation of promoter/regulatory regions has been associated with gene silencing or upregulation in tumors[9,10,11,12]. We have analyzed MGP gene methylation in different tumors using public Cancer Genome Atlas (TCGA at cancergenome.nih.gov) data repository and identified CpG sites in its promoter and first intron with clear differences in methylation status between *e.g.* healthy and prostate cancer patients providing evidence for an epigenetic regulation of MGP transcription. Furthermore, regulators of MGP such as mir155[13] also showed CpG sites differentially methylated in the same tumors. This proposal will aim to identify, through a CRISPR-Cas9 strategy, the epigenetic signatures/patterns responsible for controlling DNA methyltransferases and hypermethylation in MGP and its regulators in cancer, with a particular emphasis on prostate cancer for which we already have preliminary data, and the molecular mechanisms involved.

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