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2-Deoxy glucose regulate MMP-9 in a SIRT-1 dependent and NFkB independent mechanism

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Abstract MMP9 is a member of the family of zinc-containing endopeptidases which degrade various components of the extracellular matrix, thereby regulating matrix remodeling. Since matrix remodeling plays an important role during growth and progression of cancer and considering the fact that, tumor cells switch to aerobic glycolysis as its major energy source, this study was designed to analyze if partial inhibition of glycolysis (the major energy pathway during hypoxia) can be used as a means to control matrix remodeling in terms of MMP9 activity and expression. For this, human epithelial carcinoma cells were treated with glycolytic inhibitor, 2-deoxy glucose (2DG) at sub-lethal concentrations followed by analysis of the expression and activity of MMP2 and MMP9. The experimental findings demonstrate that exposure of cancer cells to glycolytic inhibitor at concentration that does not induce ER stress, downregulates the activity and expression of MMP9 without affecting the expression levels and activity of MMP2. Further mechanistic analysis revealed that the regulation of MMP9 was mediated in a SIRT-1 dependent mechanism and did not alter the NFkB signaling pathway. The overall results presented here, therefore suggest that the use of glycolytic inhibitor, 2DG at concentration that do not affect cell viability or induce ER stress can be an effective strategy to control matrix remodeling.

Keywords Matrix metalloproteases · 2-Deoxy glucose · Cell migration · SIRT-1 · Zymography · NFkB

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Abbreviations

2DG	2-Deoxy glucose
MMP9	Matrix metalloprotease 9
SIRT-1	Sirtuin-1
NFkB	Nuclear factor kB
ER	Endoplasmic reticulum
ELISA	Enzyme-linked immunosorbent assay
SDS-PAGE	Sodium dodecyl sulphate Poly acrylamide gel electrophoresis
NAD^+	Nicotinamide adenine dinucleotide
qPCR	Quantitative real-time PCR

Introduction

The extra cellular matrix is defined as diverse collection of proteins and sugars that surround cells in all solid tissues. This tissue component apart from providing structural support [1] also plays a major role in signaling and cell-to-cell interactions, whereby it can significantly affect diverse cell processes, such as cell cycle progression, migration and differentiation [2]. ECM is a dynamic entity which gets remodeled during different cellular processes [3, 4]. Such remodeling is regulated by a careful balance between matrix synthesis, secretion, modification and enzymatic degradation. The ECM remodeling is a tightly regulated process and is sensitive to altered expression levels of proteases, which when altered results in aberrant ECM remodeling and thereby contributing to complications associated with fibrotic diseases and cancer metastasis [5, 6].

Pronounced changes in ECM homeostasis like alterations in the normal levels of matrix remodeling enzymes, such as MMPs [7], play a crucial role in the progression and spread of tumor. Matrix metalloproteinases (MMPs)