BIOINFORMATION
Discovery at the interface of physical and biological sciences

open access www.bioinformation.net Hypothesis

Volume 9(16)

Insights from the computational analysis of CD271 glycation in mescenchymal stem cells in diabetes mellitus as a predisposition to latent tuberculosis

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Received September 07, 2013; Accepted September 08, 2013; Published September 23, 2013

Abstract:
Diabetes mellitus is considered as a predisposition factor for active tuberculosis and is known to activate the latent form of tuberculosis. However, the causative association of latent tuberculosis with diabetes is not conclusively established. Therefore, it is of interest to relate their predisposition. We describe the glycation pattern of mescenchymal stem cell surface markers as CD271+/CD45-mescenchymal stem cell is known to be associated with latent tuberculosis. We show that the lysine residues important for function of CD271 death domain are predicted to be and glycated. These observations help to discuss the role of CD271 and glycation to modulate the genesis of latent tuberculosis in chronic diabetic mellitus.

Keywords: Diabetes Mellitus; active tuberculosis, latent tuberculosis, mesenchymal stem cell markers, glycation.

Background:
Diabetes mellitus, a disease characterized by persistent hyperglycemia is a global epidemic and it is conclusively known to be associated with active tuberculosis **[1, 2].** Latent tuberculosis, the dormant form of the disease, is known to be activated if associated with Diabetes mellitus **[3].** However, diabetes mellitus is not yet established as a predisposition factor for latent tuberculosis. Currently latent tuberculosis is not recommended to be routinely screened for in diabetic individuals. In fact, a substantial controversy exist at the present moment regarding latent tuberculosis is predisposed by diabetes mellitus or not **[4, 5].** Since both diabetes and tuberculosis are common diseases a solution of this dilemma is warranted. A recent work has shown that Mycobacterium tuberculosis can stay in dormant stage inside CD271+/CD45- mescenchymal stem cells. There is enough possibility that such stem cells are niche for the tuberculosis bacterium in cases of latent tuberculosis **[6].** If diabetes mellitus is the predisposing factor for latent tuberculosis then CD271+/CD45- MSCs have to be more long-lived compared to non diabetic state. We have explored the above possibility in this work using tools of *in-silico* biology.

Methodology:
In this study we have considered CD73 (P21589), CD90 (P04216), CD105 (P17813), CD106 (P19320), CD166 (Q13740), CD146 (P43121) and CD271 (P08138) mesenchymal stem cell surface receptor markers **[7].** The sequences of the mesenchymal stem cell surface receptor proteins are taken from swissprot database and in the parenthesis the corresponding accession code of swissprot database are mentioned **[8].** It is reported that bone marrow derived CD271+/CD45- mesenchymal stem cell are a good shelter for Mycobacterium tuberculosis and perhaps such habitat is the niche for latent tuberculosis **[6].** Although mesenchymal stem cell does not express CD45 surface receptor, for the understanding of association of diabetes mellitus and latent tuberculosis, we have considered CD45 (P08575) marker protein in this study. The

functional activity and active site residues (if present) are taken from PROSITE and other databases linked with swissprot accession code. NetGlycate server is used to predict glycation sites of the proteins **[9].**

Results & discussion:

In long standing diabetes mellitus non enzymatic glycosylation of proteins (glycation) happen and this phenomenon is expected to alter biological process including inflammatory response of tuberculosis **[10-12].** It is expected that glycation pattern of CD271 will modulate latent tuberculosis since CD271/CD45- mescenchymal stem cells are proved to be the niche of Mycobacterium tuberculosis in latent tuberculosis. It is in this context we have studied the glycation of mesenchymal stem cell related proteins using in-silico tools to explore the relation of latent tuberculosis and diabetes mellitus. The function of the studied surface marker proteins of mesenchymal stem cell (as mentioned in the Methods) along with predicted to be glycated lysine residues and active site if present are given in **Table 1 (see supplementary material)**. Several lysine molecules of the studied proteins are observed to be glycated. However, it is observed that only in case of CD105 and CD271 the predicted to be glycated lysine residues resides within five residues range of the functionally important domain. It is obvious that if residues are sequentially nearer, they should also be located nearer in the three dimensional structure. In CD105, Lys402 is located nearby residues 399-401, a region whose function is predicted to be cell attachment by similarity search using in-silico tools **[13].** CD271 belongs to tumor necrosis factor superfamily. Residues ranging 344-421 constitute the death domain known by experimental studies **[14].** The residues ranging 326-341 requires for interaction with KIDINS220 as known by in-silico similarity search **[14].** Here we have observed that two predicted lysine residues, Lys330 and Lys343 are positioned just before the death domain and middle of the region which is required for interaction with KIDINS220. KIDINS220 interacts with RanBP9, a molecule critical for functioning of death domain **[14].** RanBP9 is proved to be a pro-apoptotic protein in other cells as well **[15].**

If the above observations are a reality and proved by experimental studies as well there can be glycation induced signal modification in the death receptor (CD271) in diabetes mellitus. This phenomenon has the potential to impair the death /apoptosis promoting signal transduction through the CD271 molecule of mescenchymal stem cell converting such cell comparatively long lived than non diabetic state. In that case the tuberculosis bacterium can have a longer lived stay inside the protective cover of CD271+/ CD45 – mescenchymal stem cell causing latent tuberculosis. In case such glycation causes accentuation of signal transduction process through CD271 molecule then it will make the life span of mescenchymal stem cells shorter, a phenomenon which goes against suitability of latent tuberculosis. Therefore to understand whether diabetes mellitus predisposes to latent tuberculosis or not experimental studies of glycation of CD271 death domain and its effect on the signal transduction process for apoptosis are required to be done. We recommend performing experimental study guided by these observations to solve the present dilemma.

Conclusion:

Results of this study highlights a probability of glycation of functional domain of CD271 which can occur in long standing uncontrolled diabetes mellitus. This phenomenon has the potential to modulate the life span of CD271+ mescenchymal stem cells. Since CD271+/CD45- mescenchymal stem cells are proved to be niche of Mycobacterium tuberculosis in latent tuberculosis such phenomenon has the potential to modulate the occurrence of latent tuberculosis as well. Therefore we feel that experimental verification of such result is warranted.

Author contribution:

DB and RB have developed the basic concepts. RB supervised the in-silico works. MS & SN performed the in-silico works. DB has written the paper and all the authors analyzed the data and gone through the final version of the manuscript. DB acknowledges DBT, Govt. of India for financial grant.

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Edited by P. Kangueane
Citation: **Bhattacharyya *et al.*** Bioinformation 9(16): 829-831 (2013)

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Supplementary material:

Table 1: Marker proteins and predicted glycation pattern are given.

Marker Protein (accession code)	Name of protein	Lysine residues present	Lysine residues predicted to be glycated#	Location of active sites
CD73 (P21589)	5′ nucleotidase	50,67,97,133,136,145,147,162,179,206.208 ,214,227,232,256,262,274,285,291,321,326 ,330,341,427,432,433,464,471,478,488,494 ,512,534,536,547.	67,97,179,206, 208,214,285,321,433,478,536	500-506 substrate binding region
CD90 (P04216)	Thy-1 membrane glycoprotein	21,59,60,83,87,97,126,129	83,97,126,129	-
CD105 (P17813)	Endoglin	51,86,143,216,237,280,291,347362,373,37 4,381,402,438,439,513,543,585,622	143,**402**,438,439	Cell attachment site 399-401
CD106 (P19320)	Vascular cell adhesion protein 1	4,26,70,103,106,117,131,136,154,160,171, 176,191,198,215,224,235,260,261,299,302, 311,358,390,391,394,426,442,459,464,479, 486,497,543,570,590,601,604,614,636,637, 638,647,657,661,673,692,722,726,736,738	4,26,106,117,136,154,171,191,198,260,261,2 99,302,311,394,459,486,543,590,614,736,73 8	-
CD166 (Q13740)	Activated leukocyte cell adhesion molecule	4,55,57,60,75,76,87,109,129,132,136,1421 52,153,175,189,190,208,211,231,257,261,2 69,312,318,319,368,403,404,415,419,422,4 23,431,442,472,521,527,552,553,555,559,5 63,572,573, 580	4,55,57,75,76,87,129,136,152,208,211,257,3 68,431,552,555,559,563,572,573	-
CD146 (P43121	Cell surface glycoprotein, contains Ig-like signature	47,67,69,119,134,153,176,182,185,209,214 ,217,236,251,263,286,312,398,436,439,443 ,507,551,584,585,587,595,605,616,613,631 ,640	67,134,182,185,214,251,312,551,584,585,58 7,616	-
CD271 (P08138)	Tumor necrosis factor super-family member 16	29,45,84,141,273,279,282,300, 330,343,349	29, 45, 273,**330**,**343**	344-421 death domain 326-341 interacts with KIDINS220
CD45 (P08575)	Receptor –type tyrosine protein phosphatase C	6,37,133,223,229,241,244,249,275,291,303 ,314,322,324,350,353,364,375,381,384,426 ,430,437,441,448,452,464,479.502,533,540 ,551,575.598,604,605,623,641,643,664,668 ,672,678,715,719742,759,780,785,794,800, 801,803,831,876,885,931,932,967,969,986, 993,1014,1026,1038,1052,1054,1063,1078, 1089,1093,1108,1110,1133,1143,1145,114 9,1156,1159,1200,1204,1235,1236,1243,12 52,1254,1268,1273	6,223,244,291,314,350,364,381,430,441,452, 502,533,598,604,605,672,678,759,785,794,8 85,931,967,986,993,1038,1054,1063,1110, 1145,1149,1156,1236,1243,1273	851 phospho-cysteine intermediate 1167 phospho-cysteine intermediate 819 and 895 substrate binding site

if the predicted glycated lysine residue is located within 5 residues range of the active site residues the residue is bolded.