p53-regulated long non-coding RNA PRECSIT promotes progression of cutaneous squamous cell carcinoma via STAT3 signaling

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INTRODUCTION

Long non-coding RNAs (lncRNAs) have emerged as functionally important mediators in a broad aspect of cellular regulation, from development and differentiation to emerging players in disease. They present a widely uncharacterized group of single-stranded RNA transcripts larger than 200 nucleotides in size, which interact with DNA, RNA or proteins, making them versatile regulators in all compartments of the cell. We have previously elucidated the mechanistic function of lncRNA PICSAR (p38 inhibited cutaneous squamous cell carcinoma associated lincRNA), which exerts a tumorigenic role in cutaneous squamous cell carcinoma (cSCC)^{1,2}. However, the role of lncRNAs in cSCC in general is still largely unknown.

Here we have examined the role of lncRNA LINC00346, which is specifically overexpressed by cSCC cells in culture and *in vivo*. We show that LINC00346 is regulated by p53-signaling. We demonstrate that LINC00346 regulates the expression and activity of STAT3, which in turn upregulates the expression of matrix metalloproteinases (MMPs) MMP-1, MMP-3, MMP-10, and MMP-13 and promotes invasion of cSCC cells. Based on these observations LINC00346 was named p53 regulated carcinoma-associated STAT3 activating long intergenic non-protein coding transcript (PRECSIT).

Figure 1. Expression of PRECSIT is specifically upregulated in cutaneous squamous cell carcinoma (cSCC) cells in culture and *in vivo*.

Figure 2. Expression of PRECSIT is regulated by p53.

Figure 3. PRECSIT regulates expression of activated STAT3 and matrix metalloproteinases.

CONCLUSION

- PRECSIT is a p53-regulated, nuclear-enriched long non-coding RNA with induced expression in cSCC cells compared to NHEKs
- Expression of PRECSIT is induced in cSCC and precursor lesions compared to normal skin *in vivo*
- The level of activated transcription factor STAT3 is upregulated by PRECSIT and this in turn upregulates the expression of several invasion-associated MMPs
- PRECSIT promotes progression of cSCC by specifically regulating invasion of cSCC cells *via* STAT3 signaling

Figure 4. PRECSIT knockdown inhibits cSCC cell invasion and growth of cSCC xenografts *in vivo*.

References:

1. Piipponen M, et al. *J Invest Dermatol* 136:1701-10, 2016
2. Piipponen M, et al. *Biol Open* 7:pil:bio037044, 2018

This study was supported by the Finnish Cancer Research Foundation, The Cancer Society of South-West Finland, Jane and Aatos Erkkö Foundation, Sigrid Jusélius Foundation, The state research funding of the Turku University Hospital, The Kymenlaakso Regional Fund of the Finnish Cultural Foundation, Ida Montin Foundation, Instrumentarium Science Foundation, The Paulo Foundation, The Maud Kuistila Memorial Foundation, University of Turku Graduate School Funding and Turku University Foundation.