iRHOM2-p63 pathway mediates survival and redox balance in keratinocytes

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Abstract

The palmoplantar keratodermas are characterised by different patterns of hyperproliferative thickening of the palms and soles which are often painful. We have described dominant "gain of function" mutations in RHBDF2, the gene encoding inactive rhomboid protein 2 (iRHOM2), associated with the inherited syndrome Tylosis (Palmoplantar keratoderma) with Oesophageal Cancer (TOC). Recently, we have shown that genetic depletion of iRHOM2 leads to a much thinner mammalian footpad plus decreases keratinocyte hyperproliferation and migration. As little is known about the transcriptional regulation of iRHOM2, its promoter sequence was assessed using transcription factor binding site prediction software (genomatix.gsf.de). Here, we report that iRHOM2 is a novel target gene of p63 and that both p63 and iRHOM2 can differentially regulate cellular stress associated signalling pathways in keratinocytes. In normal keratinocytes, p63 regulates positively iRHOM2 with iRHOM2 then antagonizing p63 expression whilst, in hyperproliferative keratinocytes, there is an auto-regulatory feedback loop occurring between p63 and iRHOM2. Using human TOC keratinocytes and *irhom2*^{-/-} mice, we demonstrate that p63-iRHOM2 mediated signalling regulates cellular functions including inflammation, survival and oxidative defence. For example, we identify survivin, a member of the inhibitor of apoptosis (IAP) gene family, as a novel binding partner of iRHOM2 and as a p63 target gene. In addition to increased cell survival via survivin expression, TOC keratinocytes showed increased level of reactive oxygen species (ROS) compared to control cells. We show a role for iRHOM2 in the epidermal oxidative defence response via its interaction with cytoglobin (Cygb), a reported p63 target gene. In summary our data supports therapeutic strategies targeting iRHOM2-p63 axis in hyperproliferative skin disease and dysplasia.

Results

(1) iRHOM2 is a p63 target gene

(2) Distinct regulation of p63 expression in normal and hyperproliferative keratinocytes

(3) TOC display resistance to apoptosis

(4) iRHOM2-p63 regulates apoptosis by modulating survivin

(5) iRHOM2 participates in the regulation of oxidative balance.

Conclusion

We identified that iRHOM2 is a new transcriptional target gene of p63. In the normal keratinocytes (physiological state), p63 regulates positively iRHOM2, while iRHOM2 antagonizes p63 expression. In contrast, in TOC keratinocytes (hyperproliferative conditions), an auto-regulatory feedback loop is occurring between p63 and iRHOM2. We have shown that p63-iRHOM2 signalling regulates ADAM17 activity and cellular functions including proliferation, survival and oxidative stress.

Acknowledgements

Kelsell group
Jo Huigang Zhou

P.Arcidiacono is funded by iMOVE Marie Curie Fellowship