Complement component C1r upregulates the expression of matrix metalloproteinase-1, -13 and -10 and promotes invasion of cutaneous squamous carcinoma cells

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Background

Cutaneous squamous cell carcinoma (cSCC) is the most common metastatic skin cancer and its incidence is increasing worldwide. We have characterized several complement components and inhibitors of alternative pathway that regulate cSCC progression (Riihilä et al, 2014, 2015, 2017). Our previous studies have also demonstrated the role of complement classical pathway in cSCC progression (Riihilä et al, 2019). In this study we have investigated in detail the mechanistic role of serine protease C1r, a component of the C1 complex of the classical pathway of complement system.

Figure 1. Characterization of C1r knockout cSCC single cell clones.

Figure 2. Knockout of C1r decreases proliferation, migration and invasion of cSCC cells.

Figure 3. Alteration of gene expression profile in cSCC cells after C1r knockdown.

Figure 4. Knockout of C1r suppresses growth of cSCC in vivo.

References:

- Riihilä PM, Nissinen LM et al (2014) Complement factor H: a biomarker for progression of cutaneous squamous cell carcinoma. *J Invest Dermatol* 134(2):498-506. doi: 10.1038;
- Riihilä P, Nissinen L et al (2015) Complement factor I promotes progression of cutaneous squamous cell carcinoma. *J Invest Dermatol* 135(2):579-588. doi: 10.1038;
- Riihilä P, Nissinen L et al (2017) Complement Component C3 and Complement Factor B Promote Growth of Cutaneous Squamous Cell Carcinoma. *Am J Pathol* 187(5):1186-1197. doi: 10.1016;
- Riihilä P, Viiklepp K et al (2019) Tumour-cell-derived complement components C1r and C1s promote growth of cutaneous squamous cell carcinoma. *Br J Dermatol* doi: 10.1111

Conclusion:

- C1r knockout cSCC cells show significantly decreased proliferation, migration and invasion through collagen type I, as compared to wild type cells.
- Knockout of C1r significantly suppresses growth of human cSCC xenografts in vivo.
- C1r increases the expression of MMP-1, MMP-13, MMP -10 and MMP -12.
- **These results provide new evidence for the role of C1r in regulating invasion of cSCC cells by increasing production of invasion-associated matrix metalloproteinases.**