Complement System in Cutaneous Squamous Cell Carcinoma

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Pilvi Riihilä, MD, defended her PhD thesis on April 10th, 2015 in Department of Dermatology and Venereology, University of Turku and Turku University Hospital. Opponent: Professor Annamari Ranki, MD, PhD, Department of Dermatology and Venereology University of Helsinki and Helsinki University Hospital. Supervisor: Professor Veli-Matti Kähäri, MD, PhD, Department of Dermatology and Venereology, University of Turku and Turku University Hospital, Finland. The thesis book is available at: http://urn.fi/URN:ISBN:978-951-29-6064-4

Cutaneous squamous cell carcinoma (cSCC) consists of 20% keratinocyte-derived non-melanoma skin cancers (NMSC), the incidence of which is increasing globally. cSCC is the most common metastatic skin cancer and it causes approximately 20% of skin cancer-related deaths. At present, there are no molecular markers for predicting which cSCC lesions are aggressive or will metastasize rapidly.

UV radiation is the most important risk factor for cSCC. During the development of cSCC, normal epidermal keratinocytes are transformed and form actinic keratosis (AK), which progresses to cSCC *in situ* (cSCCIS, Bowen's disease) and finally to invasive and metastatic cSCC. Inflammatory factors and cells are a part of cancer microenvironment and cSCC can develop in the chronically irritated skin or in the context of chronic inflammation.

The complement system is a central part of innate immunity and it regulates normal immunological and inflammatory processes. In this study, the role of complement system components and inhibitors were studied in the progression of cSCC in culture and *in vivo*. Elevated expression of complement factor H (CFH), complement factor I (CFI), complement component C3 and complement factor B (CFB) was noted in cSCC cells in culture. The analysis with immunohistochemistry (IHC) revealed that the expression of CFH, CFI, C3 and CFB was specifically noted in tumour cells *in vivo*. The staining intensity of CFH, CFI, C3 and CFB was also stronger in invasive cSCC than in AK or cSCCIS samples.

The knockdown of CFH, CFI and CFB with specific siRNAs decreased cSCC cell viability and migration, whereas the knockdown of C3 reduced only cSCC cell migration. Moreover, the knockdown of CFI, C3 and CFB inhibited growth of cSCC xenograft tumours established in SCID mice *in vivo*. In these tumours, CFI, C3 and CFB knockdown decreased the number of proliferating cells. Moreover, the knockdown of CFI increased local inflammation and complement activation.This study provides evidence for the roles of CFH, CFI, C3 and CFB in the tumour progression indicating these as molecular biomarkers and putative therapeutic targets of cSCC.

Fig. 1. Pilvi Riihilä (*right*) defended her PhD thesis on April 10th, 2015. Opponent was Professor Annamari Ranki and Professor Veli-Matti Kähäri served as Supervisor.

List of original publications

I. Riihilä PM, Nissinen LM, Ala-aho R, Kallajoki M, Grénman R, Meri S, et al. Complement factor H: a biomarker for progression of cutaneous squamous cell carcinoma, J Invest Dermatol 2014; 134: 498–506.
II. Riihilä P, Nissinen L, Farshchian M, Kivisaari A, Ala-aho R, Kallajoki M, et al. Complement factor I promotes progression of cutaneous squamous cell carcinoma. J Invest Dermatol 2015; 135: 579–588.
III. Riihilä P, Nissinen L, Farshchian M, Kallajoki M, Kivisaari A, Meri S, et al. C3 and Complement Factor B regulate growth of cutaneous squamous cell carcinoma (manuscript).