Roles of Novel Biomarkers in Progression of Cutaneous Squamous Cell Carcinoma

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Mehdi Farshchian defended his thesis in University of Turku, Finland on August 7th, 2015. The custos and the supervisor of the thesis was Professor Veli-Matti Kähäri and the opponent was Professor Eugene Healy from University of Southampton, UK. The thesis is available at: https://www.doria.fi/handle/10024/111863

The incidence of cutaneous squamous cell carcinoma (cSCC) is increasing worldwide due to lifestyle changes such as recreational exposure to sunlight and the aging of the population. The thesis project was planned to identify novel biomarkers for the growth and progression of cSCC. As the most common metastatic form of the cutaneous malignancy, cSCC has a risk of metastasis and invasion if left untreated. In addition, early detection of the tumour is invaluable in the patients with high risk of cSCC, such as immunosuppressed patients. Furthermore, these biomarkers could serve as therapeutic targets particularly in the patients with metastatic and unresectable lesions. The thesis project was mainly established on the extensive gene expression profiling of the primary and metastatic cSCC cells and normal human epidermal keratinocytes (NHEKs).

We found that SERPINA1, which codes for alpha-1-antitrypsin, is upregulated in cSCC cells compared to NHEKs. Immunohistochemistry analysis of the tissue microarrays, consisting of a large panel of normal skin, actinic keratosis (AK), cSCC in situ (cSCCIS), sporadic cSCC and recessive dystrophic epidermolysis bullosa (RDEB)-associated cSCC, revealed a strong expression of SerpinA1 in sporadic cSCC and RDEB-associated SCC. In addition, the expression of SerpinA1 is correlated with the malignant transformation of epidermal keratinocytes in cell culture and the progression of cSCC *in vivo*.

Given the fact that the role that Eph receptors and ephrin ligands play in different malignancies is complex, part of this thesis work was focused on investigating the role of Eph/ephrin in cSCC. EPHB2 gained our attention in this thesis project, because it revealed a significant upregulation in cSCC cells compared to NHEKs both in microarray-based gene expression profiling and next generation sequencing. Further analysis by quantitative real-time PCR verified markedly overexpression of EPHB2 in cSCC cells and tumours. EphB2 staining was significantly stronger in cSCC and cSCCIS compared to AK and normal skin. Furthermore, EphB2 knockdown inhibited growth of the cSCC in a xenograft model. EphB2 knockdown

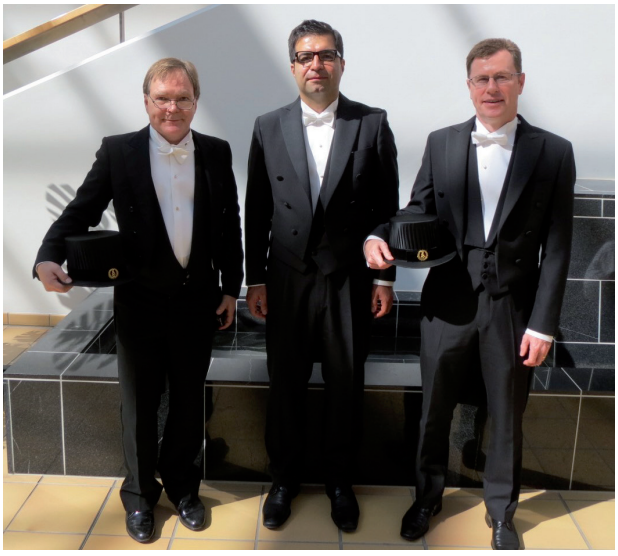

Fig. 1. Mehdi Farshchian (*middle*) defended his PhD thesis on biomarkers of squamous cell carcinoma in Turku, Finland on August 7th 2015. The opponent was Professor Eugene Healy from Southampton (*right*) and Professor Veli-Matti Kähäri (*left*) was the supervisor of the thesis.

was shown to inhibit proliferation, migration and invasion of cSCC cell lines. Inhibition of invasion-related matrix metalloproteinases (MMPs), MMP-1 and MMP-13 as a result of EphB2 knockdown could be the possible mechanism for the inhibition of the invasion of cSCC cells.

Because inflammation is involved in the development of cSCC, as the third part of the thesis project, the role of absent in melanoma 2 (AIM2) in the progression of cSCC was analyzed. Overexpression of AIM2 was observed in cSCC cell lines and tumours when compared with NHEKs and normal skin, respectively. Tumour cell-specific AIM2 expression was detected in sporadic cSCC and cSCC of the organ transplant recipients. In addition, AIM2 knockdown was shown to inhibit proliferation and invasion of cSCC cell lines and delay the growth and vascularization of cSCC tumours in a xenograft model, which

indicates the role of innate immunity and inflammation in the progression of cSCC.

In conclusion, the findings of the thesis project revealed novel biomarkers for the progression of cSCC. SerpinA1 level can be used as a simple way to diagnose cSCC in early stages. The findings on the role of EphB2 and AIM2 in the progression of cSCC identified them as attractive therapeutic targets for cSCC. This may open new horizons for the treatment of cSCC, especially metastatic and unresectable tumours. AIM2, in particular, could be a novel therapeutic target for cSCC in immunosuppressed patients.

List of original publications

I. Farshchian M, Kivisaari A, Ala-aho R, Riihilä P, Kallajoki M, Grénman R, et al. Serpin peptidase inhibitor clade A member 1 (SerpinA1) is a novel biomarker for progression of cutaneous squamous cell carcinoma. Am J Pathol 2011; 179: 1110–1119.

II. Farshchian M, Nissinen L, Siljamäki E, Riihilä P, Toriseva M, Kivisaari A, et al. EphB2 promotes progression of cutaneous squamous cell carcinoma. J Invest Dermatol 2015; 135: 1882–1892.

III. Farshchian M, Nissinen L, Siljamäki E, Riihilä P, Toriseva M, Kivisaari A, et al. EphB2 promotes progression of cutaneous squamous cell carcinoma. J Invest Dermatol 2015; 135: 1882–1892.