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Rönnstrand, Lars; Phung, Bengt

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Enhanced SOX10 and KIT expression in cutaneous melanoma

Lars Rönnstrand[1] and Bengt Phung[1,*]

[1] Lund University
Skåne University Hospital, Wallenberg Laboratory
Inga Marie Nilssons gata 53
SE-205 02 Malmö, Sweden

*bengt.phung@med.lu.se

The transcription factor SOX10 and the receptor tyrosine kinase KIT are well recognized for their importance in melanocyte development. SOX10 and KIT are also highly involved in the development of melanoma. Moreover, SOX10 has been shown to be a marker for melanocytic tumors and its protein expression can be correlated with benign nevi progression to superficial spreading melanoma but not nodular melanoma [1]. However, at present there are no studies investigating the mRNA level of SOX10 in melanoma progression.

The cell surface receptor KIT is involved in the development of melanoma and suggested to be an important oncogene in specific subtypes of the disease. Accordingly, KIT gene amplification and mutations have been found in acral melanoma, mucosal melanoma and chronic sun damaged melanoma but more importantly very rarely in cutaneous melanoma [2, 3]. The gene expression data from these studies are the key predicting that oncogenic KIT activity is pivotal in certain types of melanoma. However, Beadling et al. [2] in contrast to Curtin et al. [3], were not able to correlate elevated levels of gene expression to enhanced protein staining. Nevertheless, these are important findings establishing KIT's role in non-cutaneous melanoma. We want to further clarify the importance of KIT in cutaneous melanoma because a recent study illustrated that KIT protein increased with progression from nevi to primary cutaneous melanoma and was decreased in metastasis [4].

Data from the two largest sample data sets (accession GSE3189 and GSE8401) from the Gene Expression Omnibus (GEO) were analyzed with respect to SOX10, KIT and KIT ligand (KITL) gene expression (Fig. 1). We extracted data from these studies because they are based on clinical material and because of the large sample sizes. The first set of data (Fig. 1a-c; accession GSE3189) consists in total of 70 clinical samples and were divided into normal skin, benign nevi and primary cutaneous melanoma. We only compared the expression level between the benign nevi and primary melanoma samples due to the comparable content of melanocytes. In the second data set (Fig. 1d-f; accession GSE8401) 83 clinical samples were analyzed and divided into primary melanoma and metastatic melanoma. However, the subtype of primary melanoma was not disclosed by the original study (accession GSE8401).

SOX10 and KIT gene expression were significantly increased in the primary cutaneous melanomas when compared to benign nevi (Fig. 1a-b). In contrast, the level of KITL was not statistically different between benign nevi and primary melanoma. Further analysis of these genes in the primary and metastatic material revealed that SOX10 expression is similar in that it was increased in the metastatic melanoma and KITL was unchanged (Fig. 1d and f). However, the expression of KIT is significantly reduced in the primary melanoma group compared to the metastatic group (Fig. 1e).

To summarize, our results show the following: 1) SOX10 steadily increases during melanoma development and progression, 2) KIT expression is upregulated in cutaneous melanoma compared to benign nevi, 3) KIT expression is reduced in metastatic melanoma and 4) KITL expression does not change in melanoma progression.

Our gene expression analysis of KIT correlates very well with the Nazarian et al. study [4] using immunohistochemical detection of KIT protein. Collectively, these results show that KIT's role in cutaneous melanoma should not be overlooked and additional functional studies are warranted.

Because the source of the primary tumor (Fig. 1d-f) was not provided by the original study, our finding that KIT expression was reduced in the metastatic melanoma samples needs to be further investigated to determine the relevance of KIT expression in metastatic melanoma.

Finally, our results support the concept that SOX10 is a sensitive marker for melanoma and novelly report that SOX10 gene expression is gradually upregulated in the disease progression.

More importantly, this report clearly shows the high upregulation of KIT expression in cutaneous melanoma, a malignant subtype in which KIT was thought to be of less importance.

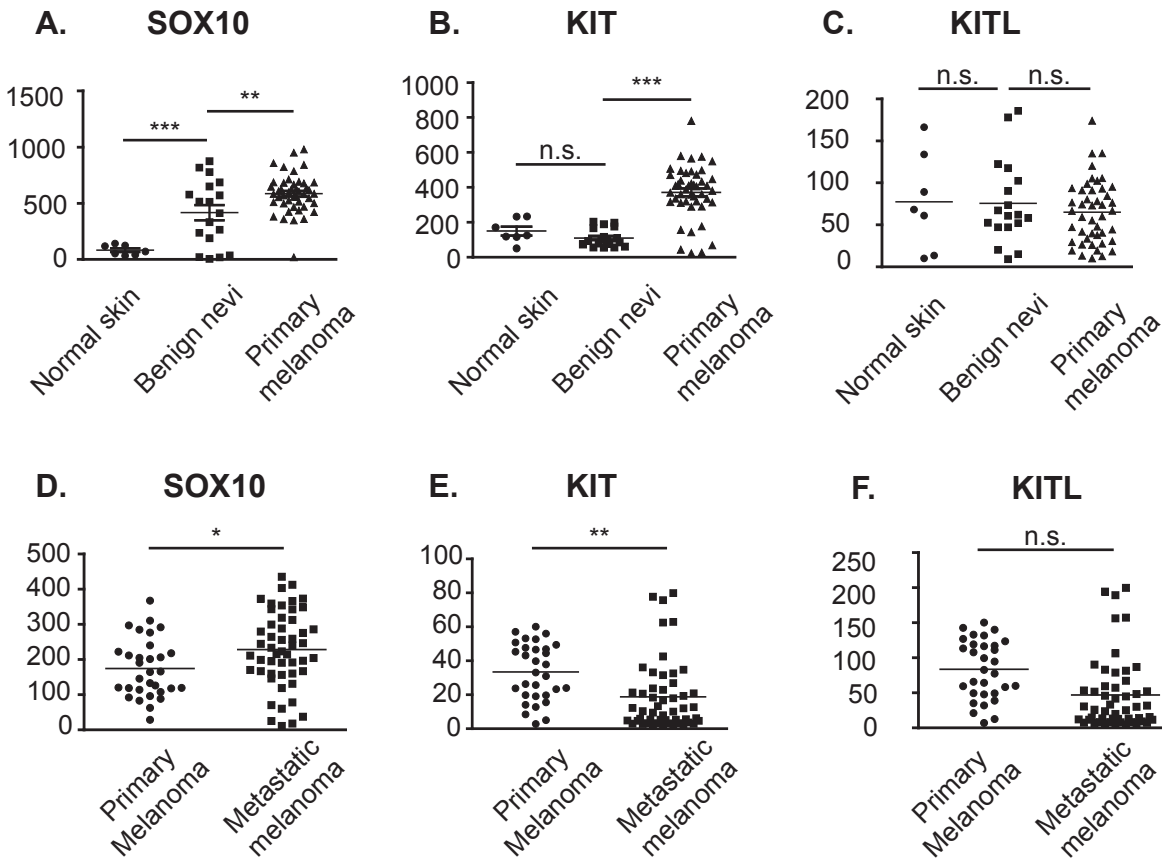
Conflict of interest

The authors declare no conflict of interest.

1. Agnarsdottir M, Sooman L, Bolander A, Stromberg S, Rexhepaj E, Bergqvist M et al. SOX10 expression in superficial spreading and nodular malignant melanomas. Melanoma Res. 2010;20(6):468-78. doi:10.1097/CMR.0b013e3283403ccd.
2. Beadling C, Jacobson-Dunlop E, Hodi FS, Le C, Warrick A, Patterson J et al. KIT gene mutations and copy number in melanoma subtypes. Clin Cancer Res. 2008;14(21):6821-8. doi:10.1158/1078-0432.ccr-08-0575.
3. Curtin JA, Busam K, Pinkel D, Bastian BC. Somatic activation of KIT in distinct subtypes of melanoma. J Clin Oncol. 2006;24(26):4340-6. doi:10.1200/jco.2006.06.2984.
4. Nazarian RM, Prieto VG, Elder DE, Duncan LM. Melanoma biomarker expression in melanocytic tumor progression: a tissue microarray study. J Cutan Pathol. 2010;37 Suppl 1:41-7. doi:10.1111/j.1600-0560.2010.01505.x.

Fig 1 a-c MRNA expression dataset collected from GEO (accession GSE3189) and analyzed with one way ANOVA and Dunnett's Multiple Comparison Test. **d-f** Data was acquired from GEO (accession GSE8401) and examined with unpaired two-tailed t test.
Statistical result is indicated as significant; * ($p \leq 0.05$), ** ($p \leq 0.01$), *** ($p \leq 0.001$) or not-significant (n.s. ($p > 0.05$)). The Y-axis display arbitrary units. Significant outlier according to Grubbs' test ($p < 0.01$) was removed from dataset.

Figure 1.


A.
SOX10
1500
1000
500
0
***
**
Normal skin
Benign nevi
Primary melanoma
B.
KIT
1000
800
600
400
200
0
***
n.s.
Normal skin
Benign nevi
Primary melanoma
C.
KITL
200
150
100
50
0
n.s.
n.s.
Normal skin
Benign nevi
Primary melanoma
D.
SOX10
500
400
300
200
100
0
*
Primary Melanoma
Metastatic melanoma
E.
KIT
100
80
60
40
20
0
**
Primary Melanoma
Metastatic melanoma
F.
KITL
250
200
150
100
50
0
n.s.
Primary Melanoma
Metastatic melanoma