Diagnostic SOX10 gene signatures in salivary adenoid cystic and breast basal-like carcinomas

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Background: Salivary adenoid cystic carcinoma (ACC) is an insidious slow-growing cancer with the propensity to recur and metastasise to distant sites. Basal-like breast carcinoma (BBC) is a molecular subtype that constitutes 15–20% of breast cancers, shares histological similarities and basal cell markers with ACC, lacks expression of ER (oestrogen receptor), PR (progesterone receptor), and HER2 (human epidermal growth factor receptor 2), and, similar to ACC, metastasises predominantly to the lung and brain. Both cancers lack targeted therapies owing to poor understanding of their molecular drivers.

Methods: Gene expression profiling, immunohistochemical staining, western blot, RT-PCR, and in silico analysis of massive cancer data sets were used to identify novel markers and potential therapeutic targets for ACC and BBC. For the detection and comparison of gene signatures, we performed co-expression analysis using a recently developed web-based multi-experiment matrix tool for visualisation and rank aggregation.

Results: In ACC and BBC we identified characteristic and overlapping SOX10 gene signatures that contained a large set of novel potential molecular markers. SOX10 was validated as a sensitive diagnostic marker for both cancers and its expression was linked to normal and malignant myoepithelial/basal cells. In ACC, BBC, and melanoma (MEL), SOX10 expression strongly co-segregated with the expression of ROPN1B, GPM6B, COL9A3, and MIA. In ACC and breast cancers, SOX10 expression negatively correlated with FOXA1, a cell identity marker and major regulator of the luminal breast subtype. Diagnostic significance of several conserved elements of the SOX10 signature (MIA, TRIM2, ROPN1, and ROPN1B) was validated on BBC cell lines.

Conclusion: SOX10 expression in ACC and BBC appears to be a part of a highly coordinated transcriptional programme characteristic for cancers with basal/myoepithelial features. Comparison between ACC/BBC and other cancers, such as neuroblastoma and MEL, reveals potential molecular markers specific for these cancers that are likely linked to their cell identity. SOX10 as a novel diagnostic marker for ACC and BBC provides important molecular insight into their molecular aetiology and cell origin. Given that SOX10 was recently described as a principal driver of MEL, identification of conserved elements of the SOX10 signatures may help in better understanding of SOX10-related signalling and development of novel diagnostic and therapeutic tools.

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Western blot analysis and antibodies. Anti-human Sox10 antibodies (NB1-68983; Novus Biologicals, Littleton, CO, USA) and cell lysates produced from snap-frozen VUMC and UVA specimens were used, as well as 13 additional specimens from MD Anderson Cancer Center specimens as described (Ivanov et al., 2012).

Immunohistochemical studies. The salivary cancer TMAs (45 1 mm cores, 14 cases in triplicates) was assembled in the laboratory of Dr Yarbrough by BB. Additional salivary cancer specimens (myoepithelial carcinoma, epimyoepithelial carcinoma, and basal cell adenoma) were obtained from the Department of Pathology, Yale School of Medicine. The breast cancer TMA that included triple-negative cases (YTMA-49–10, 0.6 mm core, n = 300) was produced by the Yale Department of Pathology. Mouse embryo slides (stage E15) were obtained from Zyggen (San Diego, CA, USA). Staining with Sox10 antibodies (goat polyclonal, N-20; Santa Cruz Biotechnology, Santa Cruz, CA, USA) was performed as described (Nonaka et al., 2008b).

RESULTS

SOX10 is a novel and sensitive biological marker for ACC and other salivary cancers that originate from the acinar region. Analysis of expression array data from grossly dissected ACC and other head and neck tumours (Ivanov et al., 2012) revealed that SOX10 was expressed in 17 out of 18 ACC specimens (~94%), including ACC xenografts produced from 11 patients (Figure 1A). SOX10 expression in primary ACC specimens was markedly higher than in normal salivary tissue (~5-fold, ACC1; ~25-fold, ACC3). SOX10 expression was maintained in the mouse ACC model reaching an ~46-fold maximum in the MAD04-385 xenograft. At the protein level, SOX10 expression was confirmed in a subset of the same specimens by immunoblotting, with GAPDH serving as a loading control (Figure 1B). Studies were extended to an independent collection of clinical ACC specimens (gift of Adel El-Naggar, MD Anderson Cancer Center, n = 13), wherein SOX10 was detected in all but one specimen (Figure 1C). Tumours examined in Figure 1A were immunostained and it was revealed that most ACC cancer cells were SOX10 positive (Figure 1D). Tumours with the lowest SOX10 expression as revealed by an expression array study were also those with the lowest percentage of tumour cells in the specimen (e.g., ACC1, ACC6, and ACC7). SOX10 staining in ACC tumour cells was intense in the nuclei and was also detectable in the cytoplasm in the majority of cells (~80–90% of cells in all tumours examined, Figure 1E). Of six MEC specimens examined, only one was SOX10 positive (MEC1, Figure 1A), but, unlike ACC, staining of this tumour revealed only moderate nuclear/cytoplasmic expression (Figure 1F). Pathological re-evaluation of this case (performed by MP) classified this case as carcinoma NOS. In line with this conclusion, this peculiar SOX10-positive MEC1 case was characterised as an outlier in our previous expression array analysis (Ivanov et al., 2012).

To explore the diagnostic value of Sox10 beyond ACC, we analysed two cases of myoepithelial carcinoma, three cases of epithelial–myoepithelial carcinoma, and one basal cell adenoma. In all these cases, Sox10 staining was observed in >80% of cancer cells. Differentiation between the myoepithelial and epithelial components in epithelial–myoepithelial carcinoma with p63, calponin, and CK7 confirmed that SOX10 is expressed in the myoepithelial component (data not shown). Sox10 is expressed in embryonic and differentiated salivary tissues. SOX10 is recognised as a marker and principal regulator of NCSCs (Britsch et al., 2001; Potter et al., 2001; Nonaka et al., 2008b). To determine whether SOX10 is expressed in developing
and mature salivary glands, mouse E15 embryonic tissue and human adult salivary and other tissues were immunostained. Presumptive acinar cells, but not ductal epithelium, expressed SOX10, suggesting that SOX10 may be involved primarily in the development and differentiation of acinar structures (Figure 2A). In line with this observation, SOX10 expression was similarly detected in the nuclei of human adult salivary gland acinar cells, as well as in the nuclei of myoepithelial cells (Figure 2B). As expected, Sox10 antibodies also stained the nuclei of melanocytes of normal skin and cutaneous MEL (Supplementary Figure 1). Altogether, these observations suggest that SOX10 has important roles in the embryogenesis and function of salivary tissue.

Sox10 expression in basal-type breast carcinoma. To better understand the significance of SOX10 expression in cancer in general and in ACC in particular, we explored SOX10 expression in 1764 publicly available U133 Plus 2.0 cancer data sets (http://biit.cs.ut.ee/mem/) using a novel noise-resistant rank aggregation and visualisation algorithm developed by Adler et al (2009) and Kolde et al (2012), which allows simultaneous comparison of gene expression across massive data sets. Robust SOX10 signatures with the involvement of hundreds of genes were detected in breast cancers (22 studies, 10\times 100,000 for top 50 genes), MEL, neuroblastoma, (Figure 3A and Supplementary Table 1), and glioma, but not in other cancers (data not shown). In breast cancer studies with stratified molecular subtypes, SOX10 and its
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signature strongly co-segregated with the basal subtype. Thus, analysis of the data set E-GEOD-21653 that compared expression profiles of basal, ERBB2, and luminal subtypes (total \( n = 266 \)) revealed that 52 of 73 basal-type specimens (71%) expressed SOX10 (Figure 3B). When compared with luminal subtypes, the basal subtype showed at least a 16-fold upregulation of SOX10 (Figure 3C, \( P < 10^{-10} \)). A similar rate of SOX10-positive BBC cases (73%) was confirmed in the other study (E-GEOD-20711, \( n = 90 \), data not shown). SOX10 expression in breast cancers was validated by immunostaining on a TMA containing normal and malignant breast tissues, including TNBCs that largely overlap with BBC (Figure 3D). In normal breast tissue, SOX10 was expressed in the nuclei of basal/myoepithelial and some luminal cells. In TNBC cancer, nuclear SOX10 expression was seen on average in \( > 60\% \) of malignant cells. Together, these data suggest that SOX10 is expressed in normal breast tissue as well as in BBC/TNBC breast cancers serving as a marker of cell identity. When our article was in preparation, SOX10

Figure 2. Immunohistochemical analysis of SOX10 expression in mouse embryonic (A) and human adult (B) salivary glands. The red arrow in A points to the developing duct, whereas the black arrow shows the acinus.

Figure 3. Characterisation of SOX10 signature in BBC. (A) Rank aggregation analysis identifies genes whose activity co-segregates with that of SOX10 in BBC, MEL and neuroblastoma (NBc = neuroblastoma cell lines; NBs = clinical specimens). Two breast cancer studies that stratify specimens by molecular subtypes are marked in a red frame. (B) SOX10 overexpression in BBC. (C) The heat map for the E-GEOD-21653 study shows SOX10 signature expression in a great majority of basal-like specimens but not in other breast cancer subtypes. (D) Validation of SOX10 expression in normal (upper panel) and malignant (bottom panel, YTMA-49-10 TNBC cases 1840 (left) and 1843) breast tissues.
expression in BBC was independently reported by Cimino-Mathews et al (2013).

**Genes commonly co-expressed with SOX10 in ACC, BBC, and MEL.** To identify critical genes that may co-function with SOX10, we performed comparative analysis of SOX10 signatures in ACC, BBC, and MEL. For each of these cancers, 160 top genes that showed the highest co-segregation with SOX10 were selected (Supplementary Table 1). A comparison of these lists revealed that ACC and BBC had 24 common genes (15%), BBC and MEL had 17 (~11%), and ACC and MEL had 5 genes in common (~3%). Remarkably, some of the genes from the ACC/BBC and BBC/MEL overlaps (Figure 4) have been previously described as markers of poor prognosis in MEL (MIA (Diaz-Lagares et al, 2011), S100A1 (Nonaka et al, 2008a; Sviatoha et al, 2010), S100B (Sviatoha et al, 2010; Diaz-Lagares et al, 2011) and SHC4/RaLP (Fagiani et al, 2007)), BBC (FABP7 (Alshareeda et al, 2012), FZD7 (King et al, 2012) and MFGE8 (Carrascosa et al, 2012)), and ACC (EN1 (Bell et al, 2012)), suggesting their utility in a plurality of cancers. However, clinical significance of four ‘core’ genes that co-segregated with SOX10 in all three cancers, ROPN1B, GPM6B, COL9A3, and MIA, as well as many other genes found in the overlaps (e.g., CDH19, PLP1, and TRIM2) remains to be explored. To our knowledge, none of these genes have been previously studied in the context of SOX10 expression.

**SOX10 signature is recapitulated in BBC cell lines.** To validate our *in silico* findings, we assessed the expression of SOX10 signature elements in A375 MEL and breast cancer luminal (MCF, T47D) and basal-like (HCC38, HCC1569, and MX-1) cell lines. In this experiment, MEL and BBC cells expressed SOX10 and its several co-expression partners that we assessed (MIA, TRIM2, ROPN1, and ROPN1B), whereas oestrogen receptor (ESR1)-positive luminal MCF7 and T47D cell lines expressed only limited amounts of TRIM2 and none of the other SOX10 signature elements (Figure 5).

**Genes whose expression negatively correlates with SOX10 expression in breast and salivary cancers.** To further explore SOX10 specificity to the basal-like breast cancer subtype, we performed correlation analyses of the TCGA Invasive Breast Carcinoma data set (Agilent mRNA expression microarrays, *n* = 547) (Cancer Genome Atlas Network, 2012) and identified FOXA1, ESR1, GATA3, XBP1, and CA12 as top-rank genes whose expression negatively correlated with SOX10 (Table 1).

**Noteworthy,** FOXA1 showed the strongest negative correlation with SOX10, and this observation was also confirmed on the E-GEOD-21653 BBC data set (Figure 6A) as well as on our ACC expression array (Ivanov et al, 2012) data set (Figure 6B). The opposing expression of FOXA1 and SOX10 was consistent with reports that FOXA1 supports luminal breast cancer morphology (Nakshatri and Badve, 2009) and suppresses the basal-like phenotype (Bernardo et al, 2013). In addition, FOXA1 cooperates with ESR1 as a pioneer factor that maintains luminal identity in

![Figure 5. Expression of SOX10 signature components in MEL and BBC cell lines.](image)

**Table 1. Genes whose expression negatively correlates with SOX10 in the TCGA-invasive breast cancer study**

| Genes       | R-value | P-value |
|-------------|---------|---------|
| FOXA1       | −0.63624 | 3.70E-62 |
| MLPH        | −0.61778 | 1.01E-57 |
| ESR1*       | −0.60447 | 1.06E-54 |
| S10T1       | −0.59409 | 1.93E-52 |
| AGR2        | −0.59118 | 8.01E-52 |
| PRR15       | −0.58674 | 6.84E-51 |
| GATA3       | −0.58602 | 9.65E-51 |
| XBP1        | −0.58458 | 1.92E-50 |
| LRFN2       | −0.57267 | 4.95E-48 |
| CYB561D2    | −0.57248 | 5.39E-48 |
| P4HTM       | −0.57196 | 6.85E-48 |
| TBCD19      | −0.56207 | 5.76E-46 |
| CA12        | −0.55819 | 3.14E-45 |
| FAAH2       | −0.55712 | 5.00E-45 |
| AR          | −0.55371 | 2.17E-44 |

*Underlined genes cooperate in ESR1 signalling.*
breast cancer (Zhang et al, 2010). Pioneer factors are chromatin remodellers with the capacity to modulate cellular identity by defining the genomic regions accessible for other transcription factors (Jozwik and Carroll, 2012). Three other genes from Table 1, GATA3, XBP1, and CA12, are each linked to the ESR1 and FOXA1 activities (Lacroix and Leclercq, 2004; Barnett et al, 2008; Nakshatri and Badve, 2009; Bernardo et al, 2010). Together, these data suggest that FOXA1 and SOX10 expression is mutually exclusive in breast and salivary cancers and is linked with maintenance of distinct molecular subtypes.

**DISCUSSION**

The transcriptional factor SOX10 appears to support stem-like properties in normal tissues and cancer cells. In normal tissue, it maintains stem cells in their undifferentiated state and controls differentiation (Wegner, 2005; Kelsh, 2006; Wong et al, 2006), whereas in MEL it serves as a marker of the stem-like CD271-positive cells (Givneni et al, 2011). In ACC, as we demonstrated previously (Ivanov et al, 2012), SOX10 expression correlates with the neural stem markers TrkC, MAP2, SALL2, and SLITRK6. In this study we establish SOX10 as a novel sensitive ACC marker, which is expressed normally during salivary gland differentiation and markedly upregulated in a great majority of ACC cells. Thus, in differentiating salivary cells and ACC, SOX10 may function in a way similar to that in differentiating melanocytes and MEL. We also characterise SOX10 as a marker of BBC, a molecular subtype of breast cancer that lacks expression of oestrogen, progesterone, and HER2 receptors (human epidermal growth factor receptor 2) (Valentin et al, 2012) and, similar to ACC, expresses basal cytokeratins (Nielsen et al, 2004) and other genes linked to myoepithelial cells (Treilleux and Morellon-Mialhe, 2009). The diagnostic value of SOX10 in BBC was confirmed by others in a recently submitted study (Gimino-Mathews et al, 2013). Unlike previously described TrkC, which is highly specific for the myoepithelial cells/cancers of salivary gland and myoepithelial cells of breast tissue, Sox10 expression in salivary tissue is not restricted to the myoepithelial cells and tumours that show myoepithelial differentiation but is also seen in acinar cells, acinic tumours, and, occasionally, in the basal cells of the intercalated duct (data not shown). Thus, Sox10 shows a broader specificity than TrkC and may be helpful for the diagnosis of salivary cancers that originate from the acinar and intercalated duct areas of the salivary gland.

Characterisation of SOX10 as a basal-like breast cancer marker in both ACC and BBC supports the hypothesis that cancer cells hijack the inherent plasticity of normal stem cells (Raouf, 2010) and stimulates more studies into the therapeutic and biological importance of SOX10 expression. Moreover, as we demonstrate here, the expression of large sets of genes strongly co-segregates with SOX10 in these cancers, greatly increasing the reliability of molecular diagnostics. These novel potential markers and targets, once validated, may significantly increase the accuracy of FNA diagnosis in ACC and BBC. Importantly, some of these genes have been already validated as diagnostic and prognostic markers.

Although SOX10 activity in MEL is essential for cell survival and growth (Shakhova et al, 2012), targeting of transcription factors is challenging. As SOX10 expression in each of three cancers appears to be part of a highly coordinated expression of hundreds of genes, a better understanding of molecular mechanisms, signalling pathways, and critical drivers that orchestrate such expression may provide a more efficient and broader means for tumour suppression. As we show, analysis of the overlaps between SOX10 gene signatures is instrumental for identification of common elements of the SOX10 network. Remarkably, two out of four genes that consistently co-expressed with SOX10, GPM6B, and COL9A3 (Figure 4) have been previously reported to bind EGFR (Deribe et al, 2009), a commonly recognised BBC marker and regulator (Carey et al, 2010). Thus, it would be interesting to explore the possible involvement of this receptor in SOX10 signalling. Two other closest SOX10 co-expression partners are ROPN1B and MIA. Although little is known about ropporin ROPN1B, its function is most likely mediated through its R2D2 motif, which is implicated in cAMP-dependent PKA signalling (Newell et al, 2008). As PKA activity is critically involved in

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**Figure 6.** Mutually exclusive expression of SOX10 and FOXA1 in breast and salivary cancers. Expression array data on head and neck cancers (A) and heat map for the E-GEOD-21653 study (B) show inverse SOX10 and FOXA1 expression in ACC and breast cancer, respectively.
melanocyte proliferation and stimulates the proliferation of MEL cells (Mantovani et al, 2008), it is essential to investigate the ROPN1B role in ACC and BBC. Unlike ROPN1, the MEL inhibitory activity protein MIA is a well-established diagnostic and prognostic serum marker and therapeutic target in MEL (Schmidt and Bosserhoff, 2009; Perrotta et al, 2010; Kluger et al, 2011; Schmidt et al, 2012). However, to our knowledge, its link with SOX10 has not been previously established. Studies on serum derived from ACC and BBC patients are warranted in order to assess the clinical value of MIA in these cancers.

Overall, our findings bring attention to previously unrecognised transcriptional networks and signalling pathways related to SOX10 activation in various cancers and help to identify common and cancer type-specific biomarkers and prospective therapeutic targets whose expression strongly co-segregate with SOX10.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.
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