Is HOTAIR really involved in neuroendocrine prostate cancer differentiation?

Long non-coding RNAs (lncRNAs) are emerging as key players in several aspects of human pathophysiology (Jain, Thakkar, Chhatai, Pal Bhadra, & Bhadra, 2017). Upon transcription, lncRNAs fold in tri-dimensional structures and can interact with epigenetic effectors, signalling proteins and other macromolecules, thereby influencing a diverse range of cellular function. However, due to the limited information available on lncRNA function and expression profiles, it is sometimes difficult to define their roles in specific diseases.

HOTAIR is an oncogenic lncRNA, which was first discovered for its role in breast cancer metastasis (Gupta et al., 2010). Successive studies have confirmed the oncogenic role of *HOTAIR* in other malignancies, including prostate cancer. As shown in figure 1A, prostate malignancies can progress through three main stages: (1) hormone-sensitive tumours, which are treatable by a combination of radiotherapy, surgery and hormonal therapy; (2) castration-resistant prostate cancer (CRPC) which is resistant to conventional androgen deprivation therapy, but can be treated by more potent hormonal drugs (enzalutamide, abiraterone); (3) neuroendocrine prostate cancer (NEPC), which is currently incurable. Clinical and experimental evidence indicates that the *HOTAIR* lncRNA drives the progression from androgen-sensitive to castration-resistant prostate cancer (CRPC) (Gupta et al., 2010).

We have previously shown that the lncRNA *MIAT* might be involved in a further step of prostate cancer progression: the trans-differentiation from androgen-independent adenocarcinomas to NEPC (Crea et al., 2016). Our analysis of clinical databases showed that MIAT expression is significantly higher in NEPC samples, compared to all other prostate cancer subtypes, and that MIAT up-regulation is associated with worse prostate cancer prognosis. NEPC is the deadliest form of prostate cancer. Hence, understanding the mechanisms underpinning this trans-differentiation is of fundamental importance. For this reason, we are currently working on the functional characterization of *MIAT* and other lncRNAs that could be involved in NEPC.

A recent experimental paper claimed that the *HOTAIR* lncRNA also plays a pivotal role in NEPC trans-differentiation (Chang et al., 2018)9944905}. The authors found that *HOTAIR* up-regulation induced the expression of some NEPC markers in prostate cancer cells, and that *HOTAIR* expression was inhibited by the transcriptional repressor REST. Since REST is down-regulated during the transition from CRPC to NEPC, the authors propose that REST silencing triggers *HOTAIR* expression in NEPC cells (figure 1A). An analysis of clinical prostate cancer samples showed that HOTAIR expression is higher in CRPC, compared to hormone sensitive malignancies. Crucially, the authors did not compare the expression of HOTAIR in NEPC vs CRPC samples.

In light of this evidence, we sought to corroborate the role of *HOTAIR* in NEPC trans-differentiation by analysing our patient-derived models and a clinically available dataset. As shown in figure 1B we found that, while REST is consistently down-regulated in NEPC vs CRPC/adenocarcinoma samples, *HOTAIR* is expressed at very similar levels in the two groups. Notably, the clinical dataset confirmed our previous findings on *MIAT*.

Based on this evidence, we propose that the protein REST plays a pivotal role in inhibiting NEPC trans-differentiation, but that this effect is not mediated by the *HOTAIR* lncRNA. We believe that further studies are needed to dissect the functional role of lncRNAs in NEPC.

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