Letter to the Editor

Serum microRNA screening for DICER1-associated pleuropulmonary blastoma.

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Abstract

CT chest scanning has been recommended to screen for pleuropulmonary blastoma (PPB) in babies and young children known to harbor germline DICER1 mutations. However, only a minority of these patients will develop PPB, and the use of CT scans is associated with risks such as secondary malignancy. Recently, we identified a panel of microRNAs that were highly abundant in the serum of a patient with a germline DICER1-mutated PPB, but present at normal levels in healthy relatives carrying the same germline mutation. Consequently, we advocate the addition of serum microRNA profiling to this programme of radiological surveillance, in order to establish its clinical utility as a PPB biomarker. If validated, this blood-based screening-tool may reduce our reliance on CT imaging.
We read with interest the article ‘Judicious DICER1 Testing and Surveillance Imaging Facilitates Early Diagnosis and Cure of Pleuropulmonary Blastoma’ [1], as it raised pertinent issues for the management of families known to carry DICER1 mutations. The authors suggest that to detect early-stage (i.e. Type I) pleuropulmonary blastoma (PPB), for which survival rates are >90% [2], children known to harbor a germline DICER1 mutation should receive CT chest scan at 3 months of age, and again at 1-2 years if the first scan is negative [1].

Although the majority of PPB patients are found to have germline DICER1 mutations, penetrance is low. The majority of mutation carriers are unaffected [3], with only 10-20% estimated to develop PPB. Consequently, any screening programmes for PPB in patients with germline DICER1 mutations needs to be as non-invasive as possible, minimizing exposure to ionizing radiation. Serum microRNA profiling may be an important addition to any programme of radiological surveillance.

Serum microRNAs show considerable promise as cancer biomarkers [4], particularly as they are highly stable and resistant to degradation [5]. We recently identified a panel of microRNAs that were more abundant in the serum of a 2-year-old female at the time-of-diagnosis of an advanced (Type III) PPB, compared with patients with other solid tumors of childhood and a non-malignant control group [6]. The patient carried a germline DICER1 mutation and the PPB cells showed a further somatic ‘hotspot’ mutation in the DICER1 RNaseIIIb domain, consistent with other reports [7]. Amongst the over-expressed serum microRNAs, there was significant over-
representation of -3p strands, in keeping with the observation that DICER1 RNaseIIIb hotspot mutations result in a -3p strand bias in affected tissues [8]. Two specific microRNAs from this panel (miR-125a-3p/miR-125b-2-3p), had highly elevated serum levels at PPB diagnosis and demonstrated early treatment-related reductions [6]. Importantly, in healthy family members with germline DICER1 mutations, serum levels of these two microRNAs were similar to the control group, suggesting that the changes in the patient were directly attributable to release of microRNAs from the PPB tumor cells into the bloodstream and not from the germline DICER1 mutation per se.

Comprehensive evaluation of the clinical utility of serum microRNAs is now warranted in two patient groups. First, as a longitudinal screening-tool in patients with germline DICER1 mutations, initially in parallel with judicious radiological imaging, to identify whether levels of PPB-specific serum microRNAs [6] are elevated in early-stage disease, where outcomes are more favorable [2]. Second, in patients presenting de novo with a lung lesion, in order to resolve diagnostic dilemmas, e.g. distinguishing PPB from developmental anomalies such as congenital cystic adenomatous malformation (CCAM) [9]. As CCAMs are not associated with germline and somatic DICER1 mutations, we hypothesize that the serum profiles obtained would not show the PPB-associated -3p strand bias.

In summary, if the utility of longitudinal serum microRNA monitoring is confirmed in a larger cohort of patients with germline DICER1 mutations, the resultant decrease in CT scans will reduce the associated radiation-risk to babies and very young children [10].


