Proteolytic degradation of BigH3 can be quantified non-invasively in serum with biomarker potential for patients with non-small cell lung cancer

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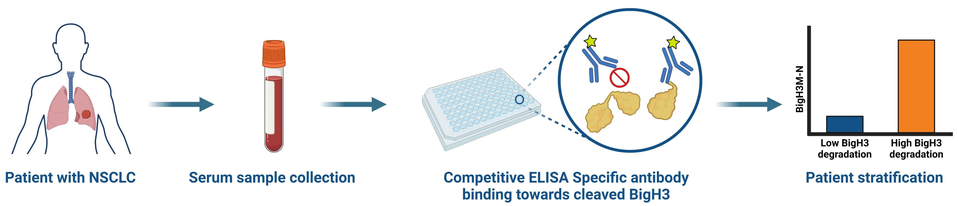
BACKGROUND

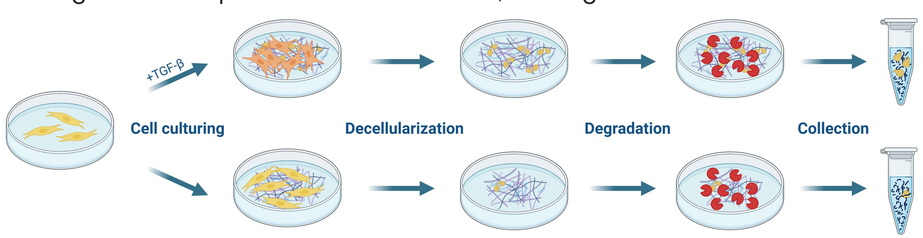
- Transforming growth factor beta induced protein ig-h3 (BigH3/TGFBI) is widely expressed and is participating in various biological processes including adhesion, migration, and angiogenesis.
- BigH3 is known to bind multiple collagens and are often embedded in the matrix where it seems to function as a linker between ECM and cell surfaces.
- The increased proteolytic activity found in non-small cell lung cancer (NSCLC) may degrade BigH3 that affect this interaction as well as generate small peptide fragments that can serve as novel non-invasive biomarkers if released to circulation.
- The aim of this study is to develop a tool to quantify degraded BigH3 non-invasively and explore its potential as a biomarker in NSCLC.

Methods

- A competitive ELISA targeting a cleaved fragment of BigH3 (BigH3M-N) was developed to reflect BigH3 degradation and enable serological quantification.
- BigH3M-N was measured in serum from a cohort of 39 patients with NSCLC (18 patients with adenocarcinoma and 21 patients with squamous cell carcinoma) and 35 healthy individuals.

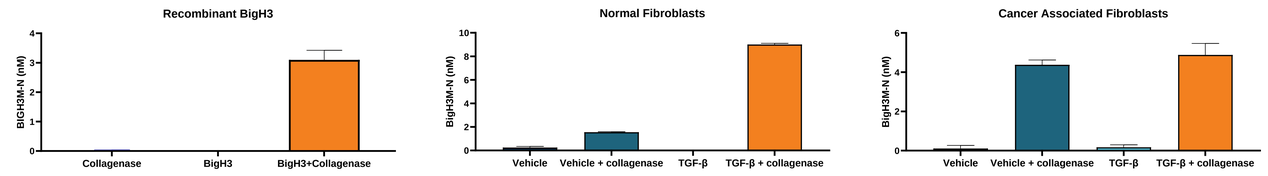


- Normal fibroblasts and cancer associated fibroblasts (CAFs) were cultured for 12 days with or without TGF-β.
- The wells were decellularized and the remaining matrix was degraded with collagenase.
- The post-degradation supernatant was collected, and BigH3M-N was measured.



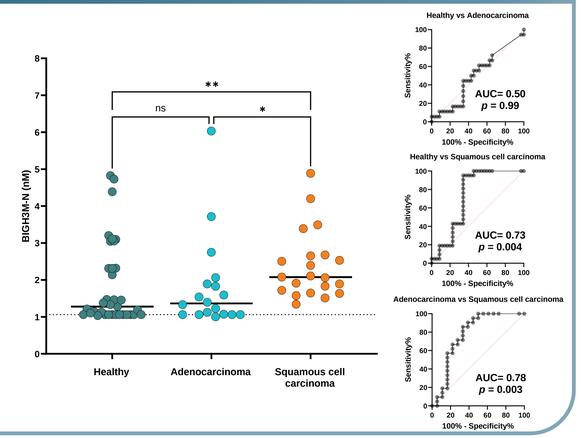
DEGRADATION OF FIBROTIC MATRIX RESULTS IN GENERATION OF BigH3M-N

- BigH3M-N was generated after incubating recombinant BigH3 with collagenase
- BigH3M-N was only detectable in collagenase degraded matrixes for both normal fibroblasts and CAFs
- A 7-fold increase of BigH3M-N was seen between the collagenase degraded matrix from fibroblasts treated with TGF-β.
- No difference in BigH3M-N levels was seen between CAFs with or without TGF-β treatment.



BigH3M-N SERUM LEVELS DIFFERS BETWEEN NSCLC SUBTYPES

- BigH3M-N was significantly elevated in serum from patients with squamous cell carcinoma (p = 0.007), but not in serum from patients with adenocarcinoma (p >0.99) compared to healthy individuals.
- There was a significant difference between BigH3M-N levels between the two NSCLC subtypes (p = 0.02).
- Serum levels of BigH3 could significantly discriminate patients with squamous cell carcinoma from both patients with adenocarcinoma (AUC = 0.78, p = 0.003) and healthy individuals (AUC = 0.73, p = 0.003), but not between patients with adenocarcinoma and healthy individuals (AUC = 0.50, p = 0.99).



CONCLUSION

- Degradation of BIGH3 can be reflected by non-invasive quantification of the cleaved fragment of BigH3, BigH3M-N, in serum.
- BigH3M-N is a promising biomarker in NSCLC with potential for discriminating between subtypes.
- As BigH3M-N is connected to fibroblast matrix biology, the optimal use for this biomarker might be in combination with other ECM biomarkers.

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