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Relevance of enhancer RNAs (eRNAs) with clinicopathological features and drug-sensitivity of gastric cancer: Evidence from bioinformatic analyses

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Abstract

Objective and background: Enhancer RNAs (eRNAs) are one of the long non-coding RNAs that are encoded from enhancer elements and involved in regulation of gene expression. In the current study, we investigated the eRNAs that were significantly correlated with clinicopathological features of TCGA gastric cancer (GC) patient cohort. Then, the association of these candidate eRNAs with anti-cancer drugs as well as the mechanism of action of those therapeutics were assessed using eRic database.

Methodology: To study the gastric-related eRNAs, the data of gastric tumors were retrieved from eRic database and those eRNAs associated with at least two clinicopathological features were then selected. The association between the target genes of the selected eRNAs and the survival of GC patients were furthermore investigated using cBioportal database. Then the list of anti-cancer drugs correlated with these candidate eRNAs were extracted from eRic database and those associated with more eRNAs were selected for further analyses.

Results: Seven eRNAs were significantly correlated with the survival of GC patients, however the genes that targeted by those, were not. Afatinib, RDEA119 and Selumetinib anti-cancer drugs were commonly associated with three of eRNAs. Our literature searches showed that these three drugs affect the RTK-Ras-MAPK signaling pathway which is one of the most important pathways in GC.

Conclusions: Our results show that the eRNAs can be independently (of their target genes) associated with the patients survival rate, thus making them as potential cancer prognostic markers. Their association with anti-cancer drugs can be furthermore utilized to investigate the mechanism of action of cancer therapeutics as well applying these data to the field of personalized medicine in order to select the best drug for each patient according to their eRNA expression profile.

Keywords: Enhancer RNAs, Non-coding RNAs, Stomach neoplasms

Introduction

Enhancer RNAs (eRNAs) are one of the long non-coding RNAs that are encoded from enhancer elements and characterized by histone marks such as H3K4me1 (Natoli et al. 2012). Functional roles of eRNAs in regulation of gene expression are depicted in Figure 1.

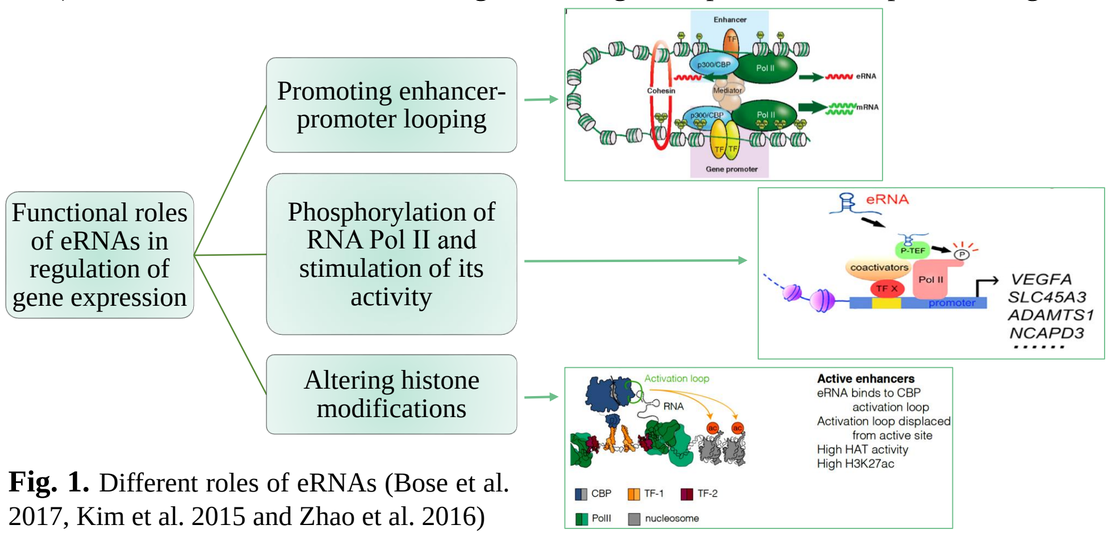
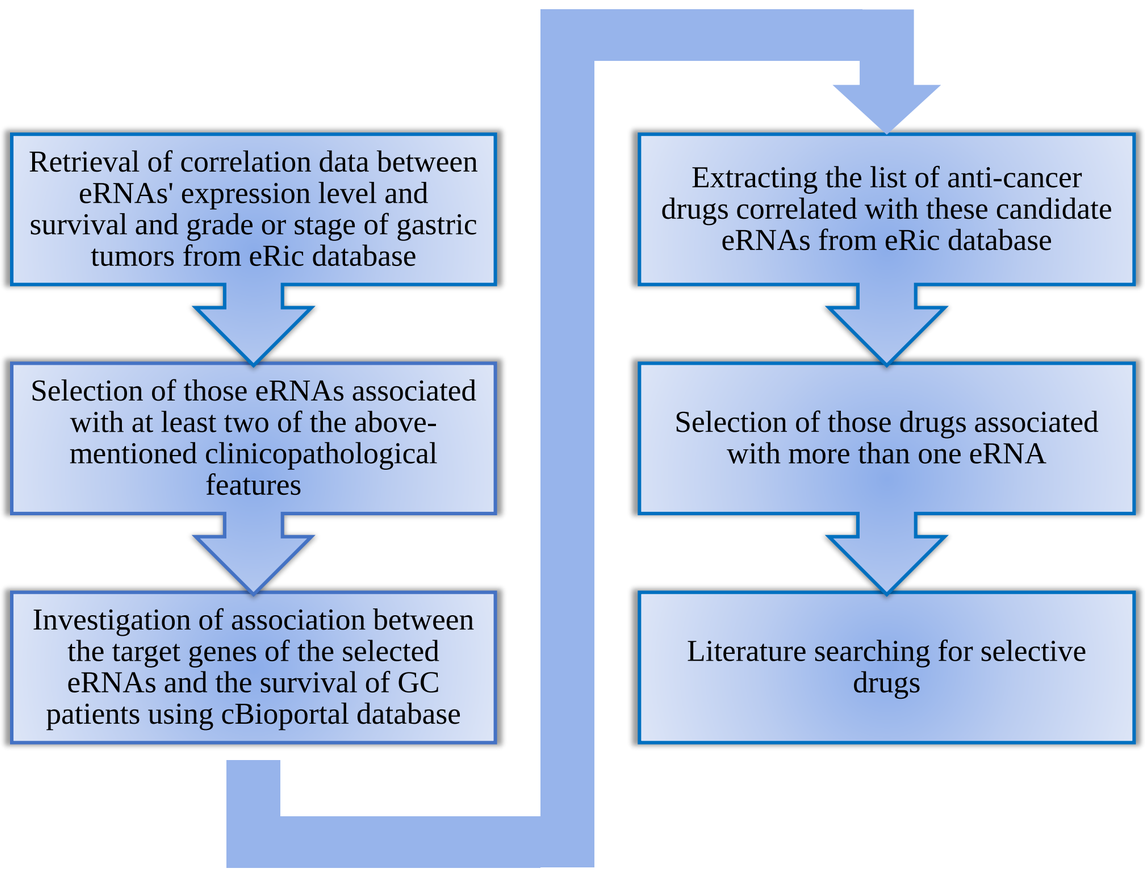


Fig. 1. Different roles of eRNAs (Bose et al. 2017, Kim et al. 2015 and Zhao et al. 2016)

Due to these functions, researchers infer eRNAs are associated with several diseases such as cancers (Ding et al. 2018). Gastric cancer (GC) is one of the most lethal cancers and the third most prevalent cancer in 2018 in Iran (Bray et al. 2018). In the current study, we investigated the eRNAs that were significantly correlated with clinicopathological features of TCGA gastric cancer patient cohort. Then, the association of these candidate eRNAs with anti-cancer drugs as well as the mechanism of action of those therapeutics were assessed using eRic database (Zhang et al. 2019).

Materials and Methods



Results

- Seven eRNAs including: ENSR00000016272, ENSR00000130536, ENSR00000140186, ENSR00000140187, ENSR00000163563, ENSR00000172804 and ENSR00000250206 were significantly correlated with the survival of GC patients (Fig. 2), however the genes that targeted by those, were not.

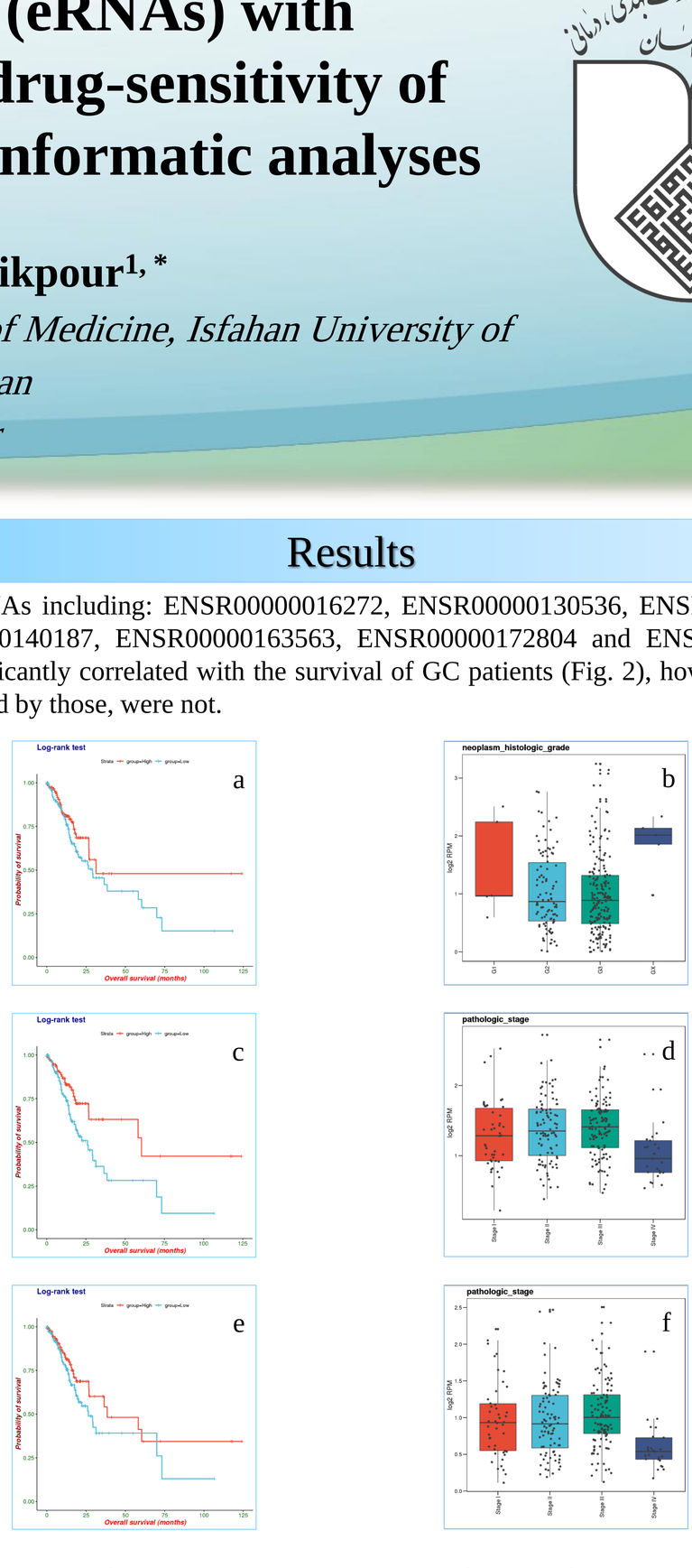


Fig. 2. Correlation of eRNAs and clinicopathological features of GC patients. For example: ENSR00000016272 is correlated with survival (FDR: 0.0327)**(a)** and grade (FDR: 0.0202)**(b)**. ENSR00000130536 is correlated with survival (FDR: 0.0096)**(c)** and stage (FDR: 0.0034)**(d)**. ENSR00000250206 is correlated with survival (FDR: 0.0377)**(e)** and stage (FDR: 0.0005)**(f)**.

- Afatinib, RDEA119 (Refametinib) and Selumetinib anti-cancer drugs were associated with three of the above-mentioned eRNAs (ENSR00000016272, ENSR00000130536 and ENSR00000250206). These drugs affect the RTK-Ras-MAPK signaling pathway which is one of the most important pathways in gastric cancer (Fig. 3)(Selim et al. 2019).

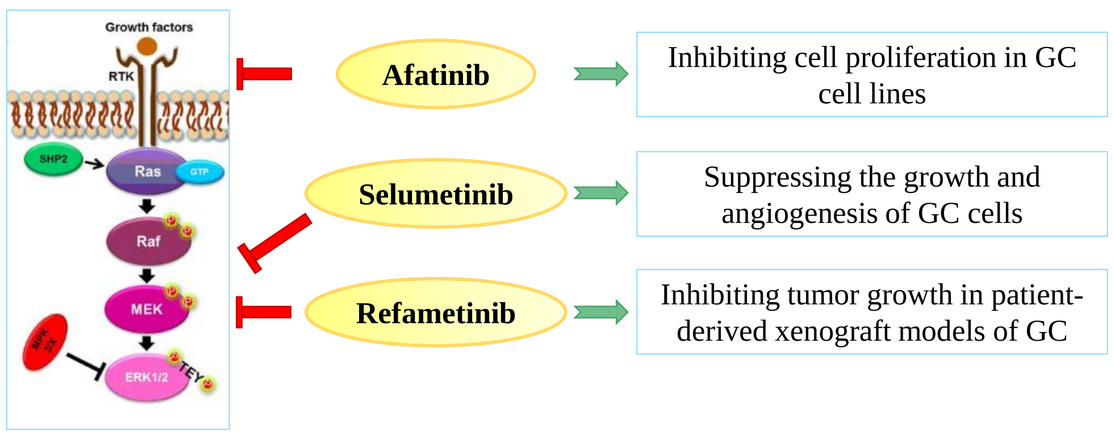


Fig. 3. The effect of three drugs on RTK-Ras-MAPK signaling pathway in GC

Discussion, Conclusion and Suggestions

Our results show that the eRNAs can be independently (of their target genes) associated with the patients survival rate, thus making them as potential cancer prognostic markers. Their association with anti-cancer drugs can be furthermore utilized to investigate the mechanism of action of cancer therapeutics as well applying these data to the field of personalized medicine in order to select the best drug for each patient according to their eRNA expression profile.

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