Stress induced miRNA changes in depression: peripheral biomarker or pathophysiology?

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Background
- Stress occurs on social, psychological and metabolic levels. If the neuro-immuno-endocrine system cannot react appropriately to the changing circumstances, maladaptive diseases occur such as major depression (MD).
- The lifetime prevalence of MD is 20%. It is a multifactorial disease: the individual vulnerability depends on environmental (stressful life events) and genetic factors (gene mutations and suspected complex gene expression regulatory dysfunction)1.
- MicroRNAs are small, non-coding RNAs, which play role in the regulation of posttranscriptional gene expression by inducing destabilisation, degradation or storage of the target mRNAs.
- MicroRNAs have special role in neural plasticity (learning), maintenance of the circadian rhythm and mechanism of antidepressants2.
- Fibroblasts are considered as in vitro neuron models since their receptor profile and signal transduction is very similar to the brain tissue3.

Subjects and Methods

1. Fibroblast cultures
- from skin biopsies of
  - patients with major depression (MD)
  - controls (CNT)

2. Metabolic stress treatment (1 week)
- STD = standard medium
- + CTL = glucose deprived, galactose enriched
- + lipid = lipid reduced, cholesterole deficient

- CNT
  - age (yrs, avg) MD age (yrs, avg)
  - CNT1 30-48 (37,5) MD1 29-46 (36,5)
  - CNT2 27-40 (32,2) MD2 26-31 (31)
  - CNT3 44-52 (49) MD3 43-52 (49,7)
  - CNT4 20-25 (21,8) MD4 22-23 (22,4)

3. Data mining – statistical analysis
- [ALR] ≥ 0.378; [ddCt] ≥ 0.583; p<0.05
- analyses of correlation between the mRNA and miRNA alterations

Discussion
1. We examined the microRNA profile of MD patients’ fibroblasts first in the literature → new possible diagnostic and therapeutic biomarkers.
2. The microRNA stress response pattern of CNT is similar after the two different metabolic stressors → proof of an evolutionary fixed adaptation scheme.
3. Individual variability of the stress reaction among CNTs is originating from genetic diversity of CNT population.
4. MD group reacts on stress differently on the level of gene expression (mRNAs) and gene regulation (microRNAs) → MD is a maladaptive pathway where the genetically impaired stress response sensitises the individuum for the environmental stressors.
5. We found similar microRNA stress reaction on populational level in MD → underlies the role of hereditary factors which may occur not only on the level of single gene polymorphism but also in complex gene expression regulation.
6. Fibroblasts can be easily gained and cultured and have similar intracellular pathways as neurons → new potential human, in vitro depression-stress models.

Our Questions and Results

1. Which microRNAs and genes are involved in the healthy stress reaction?
- Only 4 microRNAs are affected by both metabolic stress treatments. One of these is miR-146b-5p which regulates the NFκB pathway through targeting IRAK-1 mRNA. Pearson correlation showed that the overall gene expression profile after the two different treatment are similar to each other (R=0.51 and 0.43).

2. Which microRNAs are affected by stress in MD samples?
- The PCR microRNome results show that 183 microRNAs changed in the lipid reduced environment. 9 of these are known to play role in stress reaction and neural plasticity (miR-16, 18, 21, 30e, 34a, 124, 132, 134, 376).

3. How the microRNA and gene expression profile in MD differs from CNT?
- 45 microRNAs are differently expressed in the MD samples under STD circumstances. Previously 3 of these were referred as depression-associated microRNAs (miR-18, 34a and 132)⁵.

4. Which pathways are induced by metabolic stress?
- Both stress treatments activated mostly immunity regulation and cell cycle related gene-pathways both in CNT and MD groups. These changes highlight the possible neuro-immuno-endocrine pathomechanism in MD.

References

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