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Research Article

MOUSE MODEL STUDY: EARLY LIFE CHRONIC STRESS EFFECTS ON *Sox2* AND *Bcl2* mRNA EXPRESSION IN GASTROINTESTINAL TISSUES

Keziban Korkmaz BAYRAM [1,2*], Aida Nurul BAROKAH [3], Merve Hilal DÖNMEZ [3,4], Tuba Dilay KÖKENEK ÜNAL [5], Arslan BAYRAM [6]

[1]Department of Medical Genetics, Faculty of Medicine, Ankara Yıldırım Beyazit University, Ankara, Türkiye.
[2]Gene Targeting and Transgenic Models Platform, Izmir Biomedicine and Genome Center (İBG), Izmir, Türkiye.
[3]Graduate School of Health Sciences, Department of Translational Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye.
[4]Faculty of Process Sciences, Institute of Biotechnology, Technical University of Berlin, Germany.
[5]Department of Pathology, Faculty of Medicine, Ankara Yıldırım Beyazıt University, Ankara, Türkiye.
[6]GENTAN, Genetic Diseases Evaluation Centre, Izmir Türkiye.
*Correspondence: k.korkmaz.bayram@aybu.edu.tr

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ABSTRACT

Objective: Chronic stress in early life can impact the gastrointestinal (GI) tract and increase cancer risk. Studies on mouse models have shown that maternal stress can cause lasting changes in the offspring's physiology and behaviour. These changes can be observed in the GI tract, where disturbances in cellular processes, such as apoptosis, can occur. This study examined mRNA expression in the GI tissues of maternally stressed mice, focusing on *Sox2* and *Bcl2* mRNA expressions.

Materials and Methods: Pregnant *Balb/c* mice were randomly divided into three groups. The litters of the control were exposed to routine conditions. In contrast, others were randomly exposed to unpredictable maternal separation (MS) for three hours every day between 1-14 postnatal days (PND). Half of the MS dams were exposed to unpredictable maternal stress (MSUS) within these three hours. Five-week-old litters were sacrificed, and total RNA was isolated from the muscle, duodenum, and stomach tissues using the Phenol-Chloroform technique. *Sox2*, *Bcl2* and *Gapdh*, mRNA expression was measured by Rotor-Gene Q. The data obtained were analysed using One-Way ANOVA tests and Kruskal-Wallis in GraphPad Prism9.

Results: Although the *Bcl2* mRNA expression in the stomach remained unchanged, it significantly increased in the duodenum of MS ($p=0.0132$). Similarly, while the *Sox2* mRNA expression in muscle did not change substantially, it increased significantly in gastric tissue of MSUS ($p=0.0030$). Furthermore, a significant positive correlation was found between the *Sox2* and *Bcl2* genes in gastric tissue ($p=0.005$).

Conclusion: Early life stress (ELS), GI dysfunction, and cancer susceptibility may be intricately linked. Understanding the molecular mechanisms involved in cancer susceptibility may have new implications for developing interventions that can reduce the risk of developing cancer. This research may also provide insights into new strategies for treating cancer in predisposed individuals.

Keywords: Maternal Deprivation; Maternal Stress; Sox2; Bcl2; cDNA Profile; Apoptosis

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INTRODUCTION

Chronic stress, particularly during critical developmental periods in early life, has emerged as a significant factor influencing various aspects of health and disease susceptibility later in life (1). The GI tract is particularly vulnerable among the myriad physiological systems ELS affects. In mice and humans, this vulnerable gastric system's epithelium comprises glandular units that produce acid, hormones, mucus, and digestive enzymes (2). The glandular stomach is divided into two parts—antrum and corpus—with different cell ratios and turnover rates. SRY-box transcription factor 2 (Sox2) is believed to represent stem and progenitor cell compartments at the base of antral glands (3). Research has shown multipotent stem cells expressing *Sox2* in the glandular stomach (4). Our study aims to investigate how ELS affects the mRNA expression level of *Sox2* in the gastric corpus region.

The GI tract serves as a primary interface for nutrient absorption and immune surveillance and harbours a complex ecosystem of microbes crucial for maintaining overall health. Emerging evidence suggests that ELS can profoundly disrupt the delicate balance within the GI tract, predisposing individuals to a spectrum of GI disorders and potentially impacting cancer susceptibility (5).

The interplay between ELS, GI health and cancer susceptibility is fascinating and has garnered attention in recent research endeavours (5). This study uses maternally stressed mice models to gain insights into the molecular mechanisms underlying these associations.

One intriguing aspect of this research is the examination of apoptotic pathways and the expression of critical regulatory genes within the GI tract, notably *Sox2* and *Bcl2* mRNA expression. *Sox2*, a pivotal transcription factor known for its roles in embryonic development and stem cell pluripotency maintenance, has garnered interest for its potential involvement in GI homeostasis and cancer pathogenesis (6). Likewise, *Bcl2*, an anti-apoptotic protein crucial for cell survival, has been implicated in modulating apoptotic processes within the GI tract (7).

Recent investigations have begun to detect the intricate connections between cancer and apoptosis by *Sox2* and *Bcl2* mRNA expression (6). It has been observed, suggesting a potential link between ELS, altered gene expression, and GI dysfunction.
Considering these findings, understanding the impact of ELS on GI health and cancer susceptibility holds significant clinical implications. Insights gleaned from maternally stressed mice models may offer valuable avenues for developing targeted interventions to mitigate the long-term consequences of ELS on GI tract function and reduce the risk of GI malignancies (1,5). By elucidating the molecular underpinnings of these complex interactions, we can strive towards more effective strategies for promoting GI health and combating cancer in vulnerable populations. This study aimed to investigate *Sox2* and *Bcl2* genes mRNA expression in the GI tissues of the maternally stressed mouse model.

MATERIALS AND METHODS

Animals

The study was performed with five-week-old *Balb/c* mice (n=36). These mice were housed in a temperature-controlled room with a 12/12 light/dark cycle and 55% humidity. During the study, the mice had unlimited access to food and water. This study was performed according to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments, as well as the relevant guidelines and regulations (Ethics Committee Approval No. 001, 10 January 2023).

Maternal stress mouse model

This study consisted of three distinct groups: a control group (n=12), a group subjected to unpredictable maternal separation (MS) (n=12), and a group subjected to unpredictable maternal separation combined with unpredictable maternal stress (MSUS) (n=12). From PND 1 to 14, dams and litters for MS and MSUS were subjected to three hours of proximal separation per day, chosen randomly. In addition, during this separation, MSUS dams were exposed to either 20-minute restraint or 6-minute forced swim stress during the final 20 minutes of a three-hour unpredictable separation. Dams were placed in a 50-mL Falcon tube with holes for adequate air supply to induce 20 minutes of restraint stress. Dams were subjected to a forced swimming test where they swam for five minutes in a jar of cold water at 18°C (8). After weaning, the pups were raised in social groups of 3–4 mice per cage. The animals in the control group were not disturbed except for a once-a-week cage change. Mice were sacrificed at five weeks old.

RNA isolation, cDNA synthesis and quantitative PCR (qPCR) analysis of *Sox2* and *Bcl2* genes

All wet-lab experiments were conducted at the Research and Application Center (MERLAB) of Ankara Yıldırım Beyazit University. Fifty milligrams of the corpus region from the stomach, muscle from gastrocnemius lateralis and the start zone of the duodenum were removed and placed in 1 mL QIAzol Lysis Reagent (Qiagen, Germany)

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Table 1: Primer pairs that are used for target genes.

Primer	*Sequence (5′-3′*	*Amplicon Size*
Sox2	Forward: AACCCCAAGATGCACAACTC	152 bp
	Reverse: CGCGGCCGGTATTTATAATC	
Bcl2	Forward:CTGGGATGCCTTTGTGGAAC Reverse:TCAAACAGAGGTCGCATGCT	51 bp
Gapdh	Forward: CTCTCTGCTCCTCCCTGTTC	105 bp
	Reverse: TACGGCCAAATCCGTTCACA	

solution for homogenisation (Bandelin SONOPULS ultrasonic homogeniser HD 2070, Berlin, Germany). Total RNA was extracted from the stomach using the Phenol-Chloroform technique. The RNA samples were carefully preserved at a temperature of -80°C until they were ready to be used. The quantity and quality of RNA were estimated with NanoDrop 2000c (Thermo Fisher Scientific, Massachusetts, United States of America) (8). The concentration of total RNA was found to be greater than 100 ng/µl. cDNA synthesis was performed with the First Strand cDNA Synthesis Kit for RT-PCR (Roche, Netherlands) from total RNA. The acquired cDNA samples underwent a dilution process where nuclease-free water was added in a 1:5 ratio. qPCR was performed using specific primers (Table 1) and FastStart™ Universal SYBR® Green Master (Roche, Nederland) on Rotor-Gene Q (Qiagen, Germany). The PCR cycling conditions were as follows: 10 minutes at 95°C, followed by 50 cycles of 20 seconds at 95°C and 45 seconds at 60°C. The PCR experiment was repeated two times. *Gapdh* was utilised as a housekeeping gene. Ct values were used in a delta-delta-Ct (2–ΔΔCt) analysis. The data were normalised to the same scale using the average values obtained from the control group.

Statistical analyses

The mRNA expression data in control, MS, and MSUS underwent statistical analysis using one-way ANOVA or Kruskal-Wallis test. GraphPad Prism 9.1.0 (GraphPad Software, California, United States) performed Tukey's or Dunn's multiple comparisons post hoc. Data distribution was evaluated using a histogram, q-q plot, and the Shapiro-Wilk test. Outliers were identified and removed based on David C. Hoaglin and Boris Iglewicz's approach. Repeated measure ANOVA followed by Tukey's post hoc was used to analyse the weight data. Pearson's or Spearman's correlation was used to assess the relationship between the data when appropriate. All tests were set at a significance level of $p<0.05$.

RESULTS

Maternal stress modulates *Sox2* mRNA expression in stomach and *Bcl2* mRNA expression in duodenum of mice

This study examined the mRNA expression of the *Sox2* gene in stomach and muscle tissues and the *Bcl2* gene in the stomach and duodenal tissues of mice exposed to maternal stress. The *Sox2* mRNA expression was significantly higher in the MSUS group than in the control ($p=0.0030$) and MS group ($p=0.0030$) (Fig.1a). However, the mRNA expression of *Bcl2* in the stomach (Fig.1b) and *Sox2* in the muscle tissue (Fig.2b) did not show any significant change among the groups. However, *Bcl2* mRNA expression increased in duodenal tissue in both MS ($p=0.0132$) and MSUS ($p>0.05$) groups compared to the control group (Fig.2a). While there was a significant positive correlation between the *Sox2* and *Bcl2* genes in the stomach ($p=0.005$) (Fig.1c). No correlation was found between *Bcl2* mRNA expression in duodenal tissue and stomach ($p=0.76$) (Fig. 2c).

DISCUSSION

SOX proteins, first identified through the sex-determining region Y gene (Sry) are transcription factors crucial for various developmental processes (9–11). One member of this family, the SOX2 protein, is critical in maintaining cancer stem cell properties and regulating gastrointestinal development, particularly in forming the stomach and oesophagus (6,11).

In recent years, researchers have observed that different types of tumours, including lung, pancreatic, breast, colorectal, and gastric cancer, exhibit high levels of SOX2 expression (11). SOX2 expression was significantly linked with larger tumour size, high tumour histological grade, increased risk of lymph node metastasis, and the

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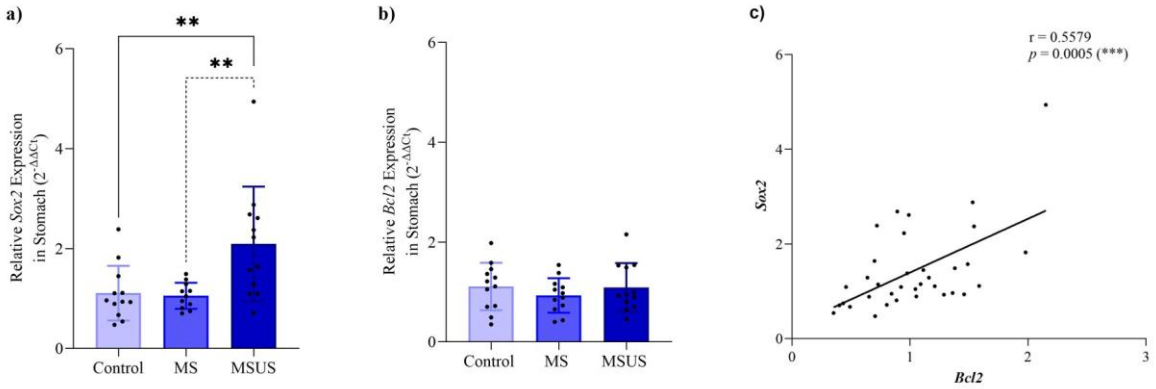

Figure 1. Comparison of *Sox2* (a) and *Bcl2* (b) mRNA expression in the stomach among the different groups. Correlation between *Sox2* and *Bcl2* mRNA profiles in the stomach (c) of the *in vivo* mouse model.

aggressive triple-negative phenotype in 1713 breast cancer patients (12). In addition, solid tumours, like hepatocellular carcinoma (HCC), may produce tumour masses due to a small group of cells known as cancer stem cells (CSC) that can increase the number of differentiated cells (6). According to the CSC hypothesis, the tumorigenicity of CSCs might be linked to the production of tumour masses due to their self-renewal and multilineage differentiation abilities (13). However, the role of SOX2 expression in gastric cancer is quite complex. Although Sarkar et al. (3) compared gastric tissues of wild-type mice with conditional *Sox2* knockout mice using tamoxifen, a selective estrogenic receptor modulator, and found no changes in gastric epithelial remodelling and differentiation. It is known that overexpression of Sox2 is oncogenic in many types of cancer. The exception is gastric cancer, in which SOX2 is a tumour suppressor (10,14).

Despite its oncogenic role in most cancers, the activity of SOX2 in gastric cancer is a topic of debate, as it may function as a tumour suppressor in certain circumstances (10,14). In a meta-analysis by Li et al. (11), 32 articles covering about 4,641 patients with gastric cancer were analysed. It was found that the expression of SOX2 was significantly reduced in cancerous tissue compared to para-cancerous tissue. This decrease in the expression of SOX2 protein was associated with clinicopathological parameters such as a shorter survival time but not with prognosis. Moreover, high levels of SOX2 expression indicate a better prognosis (11). As per Otsubo et al. (15), a decrease in SOX2 expression is linked to gastric cancer development and poor prognosis. SOX2 inhibits cell growth by inducing cell cycle arrest and apoptosis (15). Following a series of studies linking low SOX2 expression with poor patient prognosis, it has been confirmed that

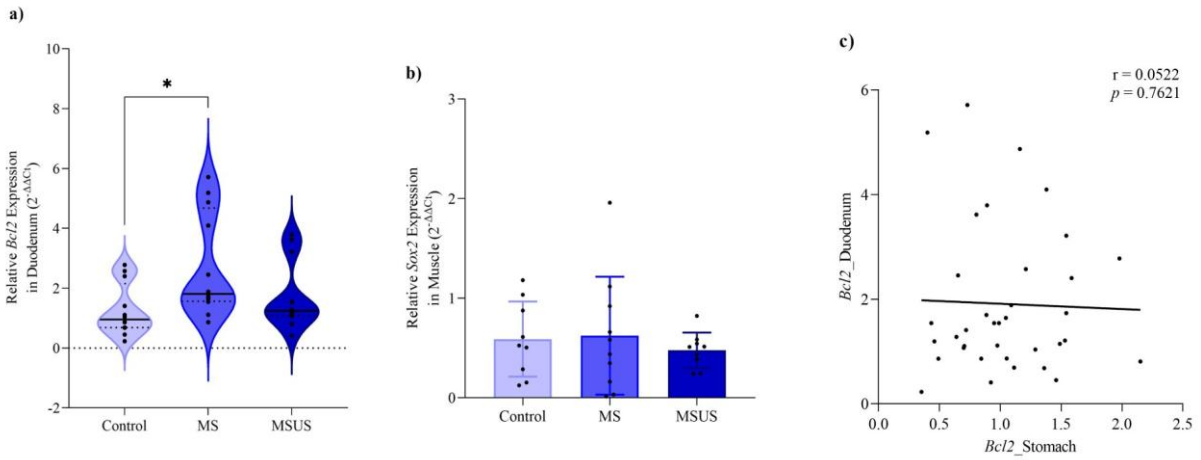

Figure 2. Comparison of *Bcl2* mRNA expression in the duodenal (**a**) and *Sox2* mRNA expression in the muscle tissues (**b**) between the groups. Correlation of *Bcl2* mRNA expression between duodenal and stomach tissue (**c**).

SOX2 inhibits proliferation, promotes apoptosis, and inhibits metastasis in vitro and in vivo (11,16). The mechanism is most likely thought to be that increased expression of interleukin 4 (IL-4) and bone morphogenetic protein-2 (BMP2) factors in gastric cancer leads to decreased SOX2 expression and increased caudal type homeobox gene 2 (CDX2) expression, causing normal gastric cells to progress towards malignant tumours (11). In this study, the mRNA expression of *Sox2* did not change in muscle tissue, but it increased in gastric tissue in litters whose dams were exposed to physical and psychological stress during early life. After exposure to chronic stress early in life, the expression of *Sox2* mRNA in the corpus region of the stomach may have increased to provide protection from stress-induced damage, adapt to stress-induced changes, or act as an early indicator of gastric cancer onset. The cells in the lining of the stomach's corpus region are unique because they contain specialised cells called gastric glands, which produce gastric acid and digestive enzymes (17). Maternal stress may initially impact the stomach, and the overexpression of the *Sox2* gene in the corpus region may be derived from multipotent stem cells. The increased expression of *Sox2* could help counteract the negative impact of chronic stress in the early stages by promoting the growth of multipotent stem cells, inhibiting proliferation, and promoting apoptosis. On the other hand, the Sox2 protein is essential for self-renewal and repairing gastric gland cells (18). Thus, *Sox2* may have assisted in repairing damage and inflammation in the stomach caused by this chronic stress.

Apoptosis is a biological process that responds to developmental cues or cellular stress. Its impairment plays a central role in cancer development (19). The *B-cell lymphoma 2 (BCL2)*, a co-regulator of apoptosis in the endoplasmic reticulum and mitochondria, can detect various types of stress (20,21). The Bcl2 protein family regulates pro- and anti-apoptotic activities. Maintaining the balance between these two activities is essential for healthy cells. However, if this balance is disrupted, it can lead to cell death or malignant cell growth (19,22). Sox2 is mainly responsible for controlling gene expression to preserve stem cells' ability to differentiate into various cell types, whereas Bcl2 prevents cell death and promotes cell survival. Sox2 and Bcl2 can have indirect connections or interactions in specific cellular environments. Despite their involvement in different cellular processes, there is no known direct functional relationship between *Sox2* and *Bcl2*. However, they may indirectly intersect through shared signalling pathways or regulatory networks. In a single study found in the literature, it was discovered that there is a relationship between *Sox2* and *Bcl2*. The study used qPCR to analyse mRNA expression levels of *Sox2* and *Bcl2* in paraffin-embedded tissues from patients with HCC. The findings revealed a significant increase in the mRNA expression levels of *Sox2* and *Bcl2*. A significant positive correlation was also observed between the two (6). This study was conducted using only male mice, which limits the generalizability of our findings to females. Future studies should include both sexes to investigate potential sex-specific differences. Our research has shown that the levels of *Sox2* mRNA expression in the stomach and *Bcl2* mRNA expression in the duodenum of litters exposed to chronic stress caused by early maternal separation and maternal stress have increased significantly. We also found a positive correlation between *Sox2* and *Bcl2* mRNA expression in gastric tissue. These findings support the results on HCC, the only known research in the literature that discusses the connection between *Sox2* and *Bcl2*. The positive correlation between these genes in HCC and maternal stress may result from regulating a common epigenetic mechanism, albeit in different tissues from different organisms. On the other hand, maternal stress may have similarly increased *Sox2* and *Bcl2* expression and predispose to cancer development.

Chronically stressed individuals may anticipate stress and exhibit a rapid cortisol response (23). This may increase individuals' vulnerability to oxidative stress (OXS). OXS characterized by an imbalance between the production of reactive oxygen species (ROS) and antioxidant defences, can result in ROS-induced damage to DNA, proteins, and lipids, ultimately leading to cellular damage and inflammation (24). Chronic inflammation, with its persistent activation of the immune system, contributes to cancer development (25). While the exact mechanisms linking SOX2 to oxidative stress warrant further investigation, SOX2 has been shown to contribute to an aggressive, oxidative tumour phenotype with enhanced drug resistance and metastatic potential in melanoma (27). This study observed significantly increased *Sox2* and positively correlated *Bcl2* mRNA expression levels in the stomachs of the MSUS group. These findings suggest that chronic maternal stress in early life may increase oxidative stress and inflammation, potentially predisposing individuals to diseases such as gastric cancer later in life.

Researchers have found that exposure to chronic stress during childhood or adolescence can have long-lasting effects on the body's stress response systems and immune function (28,29). Chronic stress can trigger the release of stress hormones such as cortisol, adrenaline, and inflammatory cytokines, signalling molecules in the immune response. When stress becomes chronic, these hormones and cytokines can disrupt the immune system, leading to persistent low-grade inflammation (30). Early

chronic stress may be so damaging to the stomach that *Sox2* is trying to compensate for this damage by overexpressing. Despite this compensation of *Sox2* overexpression, individuals may be more susceptible to gastric cancer. New studies can be planned by conducting more in-depth family histories about the early life of patients diagnosed with gastric cancer.

CONCLUSION

Despite technological advancements, the reasons behind the rising incidence of cancer in the population are still unclear. Some individuals may be more prone to cancer due to the chronic stress they experience early in life. The mRNA expression of *Sox2* and *Bcl2* in GI tissues such as the stomach and duodenum shows a significant positive correlation due to maternal stress exposure. Thus, we suggest that chronic maternal stress during infancy may increase oxidative stress and inflammation, potentially making individuals more susceptible to diseases such as gastric cancer later in life. In future studies, it would be essential to consider family history when exploring whether patients diagnosed with gastric cancer were exposed to chronic stress, such as maternal separation and maternal stress, during the first months of their lives, such as the breastfeeding period.

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Authorship contributions
The study was a collective effort of all the authors. K.K.B. and A.B. have organized and obtained financial support. K.K.B., A.N.B., and M.H.D. performed mouse models, prepared the samples, and analysed the mRNA expression. A.N.B. prepared figures and graphs and performed statistical analysis. K.K.B., A.B., and T.D.K.U. created project hypotheses, interpreted data, reviewed the literature, and prepared the manuscript. All authors read and agreed to the published version.

Data availability statement
If all authors agree to share their data, the corresponding author should be contacted to obtain it confidentially.

Declaration of competing interest
The authors in this work declare that they have no financial or non-financial interests that could compete with the described work.

Ethics
The research activities were performed according to the ethical standards outlined in the 1964 Declaration of Helsinki and its subsequent amendments, as well as the relevant guidelines and regulations (NESA Experimental Animals Laboratory Ethics Committee Approval No. 001, 10 January 2023).

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