Concept Paper

Its Time to Consider the Lost Battle of Microdamaged Piezo2 to E. Coli when it Comes to Early Onset Colorectal Cancer

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Its Time to Consider the Lost Battle of Microdamaged Piezo2 to *E. Coli* when it Comes to Early Onset Colorectal Cancer

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Abstract: Recent identification of early onset mutational signatures with geographic variations is a significant finding by Diaz-Gay et al., since early onset colorectal cancer (CRC) has emerged as an alarming public health challenge in the past two decades and we are in the dark in regards to the pathomechanism. Environmental risk factors, including lifestyle and diet are highly suspected. This is why identifying colibactin of Escherichia Coli as a potential pathogenic source in this study is one major step forward in the direction to cope with this very recent public health obstacle of our lives. Therefore, the following commentary could explain the pathomechanism and the critical role of acquired Piezo2 channelopathy that likely skews proton availability and proton motive force regulation on the side of E. Coli within the microbiota. Mechanotransduction is miraculous when it comes to converting external physical cues to inner chemical and biological ones. Correspondingly, the proposed quantum mechanical free-energy stimulated ultrafast proton-coupled tunneling, initiated by Piezo2, seems to be the principal and essential underlying novel signaling that is likely lost in colorectal cancer, hence not only contributes to cancer initiation, lost circadian rhythms, but to proliferation and metastasis as well.

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Recent identification of early onset mutational signatures with geographic variations is a significant finding by Diaz-Gay et al., since early onset colorectal cancer (CRC) has emerged as an alarming public health challenge in the past two decades and we are in the dark in regards to the pathomechanism [1]. Environmental risk factors, including lifestyle and diet are highly suspected [1,2]. This is why identifying colibactin of Escherichia Coli as a potential pathogenic source in this study [1] is one major step forward in the direction to cope with this very recent public health obstacle of our lives, therefore the following commentary could explain the pathomechanism and the critical role of acquired Piezo2 channelopathy to help this challenge.

A recent paper theorizes that there is an unaccounted underlying quantum mechanical free-energy stimulated ultrafast long-range proton-coupled oscillatory synchronizational pathway to the hippocampus from the enterochromaffin cells, e.g. from the colon and rectum [3]. Moreover, this manuscript also proposes that the intact microbiota-gut-brain axis is likely accountable for a novel synchronizational mechanism of the circadian rhythm from microbiota to hippocampal memory formation [3]. This ultrafast signaling regulation of the circadian rhythm suggested to be initiated by activated Piezo2 induced proton motive force with the involvement of VGLUT3 through allosteric transmission at a distance [3]. Noteworthy that no other proprioceptive ion channel, other than Piezo2, could initiate this ultrafast concerted proton tunneling [3]. Hence, the acquired channelopathy of Piezo2 along the aforementioned underlying ultrafast long-range proton signaled microbiota-gut-brain axis may pose a critical impairment, not to mention dysbiosis [3]. Important to note that lifestyle and dietary factors influence the circadian clocks, not to mention that circadian

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rhythms are vanished in human CRC, as patient-derived organoids-based research shows [2]. Furthermore, this finding is highly in line with the acquired Piezo2 channelopathy induced disrupted VGLUT3 signaling along the microbiota-gut-brain axis [3]. Even more importantly, this circadian clock disruptions triggers transformation by driving *APC* loss of heterozygosity, leading to Wnt signaling hyperactivation [2]. The relevance of Wnt signaling in reference to acquired Piezo2 channelopathy, and wound healing, has been emphasized earlier as well [4]. Moreover, Diaz-Gay et al. also associate colibactin exposure to *APC* driver mutations in early onset CRC [1].

Colibactin is the genotoxic metabolite product of E. Coli. E. Coli has the feature of regulating proton motive force depending on bacterial growth phases in order to sustain cell energy balance during fermentation regardless of various carbon sources [5]. Acute Piezo2 channelopathy is suggested to be a transient non-contact microdamage with an underlying proton affinity switch, however repeated bout effect of this non-contact injury without adequate regeneration periodization could chronify Piezo2 channelopathy [6]. This chronic state will likely skew proton availability and proton motive force regulation on the side of E. Coli within the microbiota due to the fermentative energy-limited conditions. This will lead eventually to impaired homeostatic energy balance equilibrium within the symbiotic microbiota-host interaction, equivalent of dysbiosis. Therefore, under this chronic energy scarcity, in which the Piezo2 containing enterochromaffin cells and somatosensory neurons are competitively disadvantaged, a vicious circle may prevail, leading to accelerated aging that includes cancer development by uncontrolled growth, depending on environmental risk factors and genetic predisposition [6]. Polyketide synthase-positive (*pks*$^{+}$) E. Coli is likely a central player in this pathomechanism [1].

Interesting proposition is the imprinting of SBS88 and ID18 during upbringing on the epithelium of the colon in the presence of *pks*$^{+}$ bacteria, but the loss or gain of these bacteria decades later [1]. Important consideration that prolonged stretch, or excessive distention, may microdamage Piezo2 [6] and this could have relevance in the colon and rectum as well. This acquired channelopathy of Piezo2 was coined as the primary damage, or one principal gateway to pathophisiology [6]. Even more importantly, this microdamage was also envisaged as a principal transcription activator [7]. Consequently, acquired Piezo2 channeloapthy induced simultaneous transcription activation and dysbiosis may explain the proposition of Diaz-Gay et al.

In support, PIEZO2 is remarkably elevated in colon cancer [8]. The current author translates this phenomenon as a feed-forward compensatory upregulation due chronic Piezo2 channelopathy. Unfortunately, this increased PIEZO2 presence promotes even proliferation and metastasis of colon cancer, beyond its role in the occurrence and development of this cancer type [8]. It should be emphasized, in regards to the aforementioned Piezo2initiated quantum mechanical free-energy stimulated ultrafast long-range proton-coupled oscillatory synchronizational pathway to the hippocampus from the enterochromaffin cells [3], that the hippocampus is not only the prime location for learning and memory, but for adult hippocampal neurogenesis as well and the ‘switched’ or ‘miswired’ secondary compensatory signaling may explain the promotion of proliferation and metastasis [9]. Furthermore, the involvement of Piezo1 activation should be contemplated in neighouring cells within the compartmental micromilieu due to the impaired/lost Piezo2-Piezo1 crosstalk [6]. Indeed, mechanical forces through Piezo1 signaling has a role within gastrointestinal tumors when it comes to tumor growth and metastasis [10].

One more additional consideration is the overloading of the gut-eye axis and its link to the microbiota. Noteworthy, that Piezo2 is also present on the cornea and retina, and likely initiates the ultrafast proton-based signaling underlying the eye-brain axis, where the hippocampus is the integrative hub [3,6]. Hence, the integration of the eye-brain axis and the microbiota-gut-brain axis through the hippocampus would explain the so-called gut-eye axis. Visible light is synchronized to our inner clock of the suprachiasmatic nuclei of the hippothalamus within the solar 24-hour cycle [11]. However, the short wavelength blue light, out of the visible light spectrum, is the strongest contribution to circadian system synchronization [11]. Accordingly, blue light exposure prior to sleeping has detrimental effect on the circadian system [11]. Therefore, the rapidly increasing

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exposure to blue light emitting devices right before sleep in the past two decades may contribute to the degradation of the gut-eye axis and increased incidence of early onset CRC.

The current commentary is in appreciation of the significant finding of Diaz-Gay et al. and aiming to promote future angle of science and research in order to confront with the mysteriously rising tendency of early onset CRC in the past two decades. Mechanotransduction is miraculous when it comes to converting external physical cues to inner chemical and biological ones. Correspondingly, the quantum mechanical free-energy stimulated ultrafast proton-coupled tunneling, initiated by Piezo2, seems to be the principal and essential underlying novel signaling that is likely lost in colorectal cancer, hence not only contributes to cancer initiation, lost circadian rhythms, but to proliferation and metastasis as well.

Conflicts of Interest: The author declares no competing interests.

Author Contributions: The author confirms the sole responsibility for the conception of the current paper and manuscript preparation.

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