

Concept Paper

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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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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 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 opinion manuscript is aiming to depict the likely onset of pathomechanism and the critical role of acquired Piezo2 channelopathy in early onset colorectal cancer that skews proton availability and proton motive force regulation on the side of E. Coli within the microbiota-host symbiotic relationship. 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 could be lost in colorectal cancer onset, hence not only contributes to cancer initiation, lost circadian rhythms, but later to proliferation and metastasis as well.

Keywords: early onset colorectal cancer; Escherichia Coli; Piezo2; hippocampus; hippocampus; circadian rhythm; proton

1. Introduction

Recent identification of early onset mutational signatures with geographic variations is a significant finding by Diaz-Gay et al., since early-onset colorectal cancer (eCRC) 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.

In support, earlier finding showed important interrelation, namely there is a clear age dependence in the microbial feature between eCRC (<50 years) and late-onset colorectal cancer (lCRC) (>65 years) [3]. Moreover, the microbial-host link was stronger in eCRC, implicating a more direct association to tumorigenesis through an unidentified cancer-related pathomechanism in contrast to lCRC [3]. Noteworthy, that age-dependent epidemiological variations in colorectal cancer (CRC) likely associated with difference in environmental factors, rather than genetic predisposition [4,5]. These factors involve lifestyle exposures, such as dietary intake, physical activity, alcohol consumption, obesity and the disruptions of the circadian rhythms in the eCRC affected younger age-group [6].

The following opinion manuscript is aiming to depict the onset of the aforementioned mysterious pathomechanism of CRC, especially ∞ CRC, and the critical role of acquired Piezo2 channelopathy. Important to note that the principality of Piezo2 is not only presented in proprioception, as demonstrated by the team of Nobel laureate Ardem Patapoutian [7], but also suggested to be present in its microdamage as a principal gateway to pathophysiology, potentially even leading to cancer [8].

2. Piezo2 Channelopathy, Dysbiosis and Circadian Rhythm

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 [9]. Moreover, this manuscript also proposes that the intact microbiota-gut-brain axis is likely accountable for a novel synchronizational mechanism towards ultradian and circadian rhythms from rhythmic bacteria of the microbiota to hippocampal memory formation [9]. The ultrafast signaling regulation of the ultradian rhythm suggested to be initiated by activated Piezo2 induced proton motive force with the involvement of VGLUT3 through allosteric transmission at a distance [9]. Noteworthy that no other proprioceptive ion channel, other than Piezo2, could initiate this ultrafast concerted quantum mechanical proton tunneling [9]. 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 the impact of dysbiosis [9]. Important to note that lifestyle and dietary factors influence the circadian clocks, not to mention that circadian rhythms are vanished in human CRC, as patient-derived organoids-based research shows [2].

In support, some of the gut bacteria within the microbiota exhibit rhythmic oscillations in synchrony to the circadian clock [10,11]. They are coined as rhythmic bacteria, incorporating approximately 10-15 % of gut microbial bacteria [10,11]. Recently it was hypothesized that these rhythmic bacteria contribute to dysbiosis at disease onset [12]. Correspondingly, circadian-related diseases were analyzed in respect to this link, such as type 2 diabetes, hypertension, atherosclerotic cardiovascular diseases, inflammatory bowel disease, metabolic syndrome, and most importantly colorectal cancer [12]. In fact, the relationship was detected between rhythmic bacteria and circadian-related diseases, although this association was weak [12]. Conclusively, these rhythmic bacteria are part of a more complex pathophysiology when it comes to circadian disruptions on the way to disease onset [12]. Part of this complexity that these rhythmic bacteria were vast minority among the most abundant bacteria, reflecting that not only circadian disruption affects them, but other physiological stressors as well [12]. Thereby, the author of this manuscript proposes that this finding is highly in line with the acquired Piezo2 channelopathy induced disrupted VGLUT3 signaling along the microbiota-gut-brain axis [9].

Furthermore, at the aforementioned current paper also theorized that Piezo2 containing enterochromaffin cells (EC) may initiate a novel ultrafast proton-based cross-frequency coupled oscillatory synchronizational signaling mechanism at the ultradian domain of the the gut-brain axis in order to provide circadian encoding of hippocampal learning and memory [9]. Moreover, ECs also interact with oscillatory serotonergic enteric neurons within the enteric nervous system and this pathway initiates a slower circadian rhythm domain of the gut-brain axis towards circadian encoding [9]. The former glutamatergic signaling likely modulates the rapid eye movement (REM) sleep, while the latter serotonergic one the non-REM sleep respectively [9].

Even more importantly, the implicated circadian clock disruptions triggers transformation by driving APC loss of heterozygosity, leading to Wnt signaling hyperactivation [2]. Noteworthy that chronic Piezo2 channelopathy induced switch/miswiring is proposed to result in a state of “part of wound healing kept alive”[13], leading to a pathological remodeling [14] with the involvement of WNT signaling [15].

3. Colibactin, Escherichia Coli and Piezo2

Diaz-Gay et al. also associated colibactin exposure to APC driver mutations in *eoCRC* [1]. In support, not only the impaired protective function of microbiome may count in dysbiosis, but the resultant increase in cancer promotion [3]. Moreover, it is suggestive that microbial signaling also affects the host by gene expression coupled mechanism [16], likely leading to microbiota induced genomic instability in CRC [17]. The current author proposes that this genomic instability is likely the result of acquired Piezo2 channelopathy due to its principle transcription activator feature [18].

Colibactin is the genotoxic metabolite product of *Escherichia Coli*. (*E. Coli*) and *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 [19]. 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 this proton affinity switch, the equivalent of chronic Piezo2 channelopathy [20]. 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 [20]. Polyketide synthase-positive (*pks*⁺) *E. Coli* is likely a central player in this pathomechanism [1].

In support, *E. Coli* strains under certain growth stage are prone to proton motive force generation [19]. This built up of proton motive force, depending on the growth stage of *E. Coli*, likely cause a proton affinity switch on the Piezo2 content of EC cells, leading to acquired Piezo2 channelopathy. Moreover, Piezo1 is demonstrated to contribute to forced-induced ATP secretion [21]. The current author suggests an analogous ATP secretion mechanism in Piezo2 as well. In addition it is worth to consider from the ATP secretion aspect that a Piezo2-Piezo1 crosstalk exist in a given fluid-filled compartment with selective barrier, like the gut is one [9]. Correspondingly, Piezo activation induced ATP efflux may serve the ATPase of *E. Coli* for proton motive force generation. Hence the switch of the growth phase of *E. Coli* will likely result in the upregulation of OXPHOS in EC cells and attached Piezo2 containing glutamatergic neurons as well. However, over time OXPHOS will be depleted as a direct result of the proton affinity switch, leading to a metabolic switch of Piezo2 containing EC cells and glutamatergic neurons, like in the case of DOMS where it is also theorized that the depletion of OXPHOS result in a neural metabolic switch, too [22].

However, in colorectal cancer the upregulated OXPHOS promotes cell proliferation and tumorigenesis, e.g., through the Prohibitin 2 – NADH:ubiquinone oxidoreductase core subunit S1 pathway mediation [23]. And this is why the dual inhibition of OXPHOS and glycolysis have synergistic antitumor effect in colorectal cancer [24]. Nevertheless, not because of preventing metabolic switch, because according to the current author the metabolic switch is already an underlying factor in colorectal cancer as part of the primary damage or Piezo2 channelopathy. Accordingly, dual inhibition of OXPHOS and glycolysis shifts the metabolic loading to a lower energy generation pathway among parallel metabolic pathways. Hence, this strategy does not feed metabolically the Piezo2 microdamaged switched/miswired rapid (not ultrafast anymore) glutamatergic VGLUT3 containing neural signaling. Therefore, proton affinity switch could switch mitochondrial energy metabolism to mitochondrial glucose and glutamine fermentation pathways from the evolutionarily superior energy-generating OXPHOS and glutamine respiration pathways [22]. In support, this glucose and glutamine respirofermentation could run simultaneously in fast growth micromilieu, like in cancer [25].

Interesting proposition is the imprinting of SBS88 and ID18 during upbringing on the epithelium of the colon in the presence of *pks*⁺ bacteria, leading to the loss or gain of these bacteria decades later [1]. Important consideration that prolonged stretch, excessive stretch/distention or chemical

destruction, may microdamage Piezo2 [20] 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 pathophysiology [20]. Even more importantly, this microdamage was also envisaged as a principal transcription activator [18]. Consequently, acquired Piezo2 channelopathy induced simultaneous transcription activation with the aforementioned memory dimensions and later in life dysbiosis may explain the proposition of Diaz-Gay et al.

In support, PIEZO2 is remarkably elevated in colon cancer [26]. The current author translates this phenomenon as a feed-forward compensatory upregulation due to chronic Piezo2 channelopathy. Unfortunately, this increased PIEZO2 presence likely promotes even proliferation and metastasis of colon cancer, beyond its role in the occurrence and development of this cancer type [26]. It should be emphasized, in regards to the aforementioned Piezo2 initiated quantum mechanical free-energy stimulated ultrafast long-range proton-coupled oscillatory synchronizational pathway to the hippocampus from the EC [9], 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 [22]. Furthermore, the involvement of Piezo1 activation should be contemplated in neighbouring cells within the compartmental micromilieu due to the impaired/lost Piezo2-Piezo1 crosstalk [20]. Indeed, mechanical forces through Piezo1 signaling has a role within gastrointestinal tumors when it comes to tumor growth and metastasis [27].

4. Blue Light

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 as the underlying backbone of the eye-brain axis, where the hippocampus is the integrative hub [9,20]. Photoreceptors in the eye, called retinal ganglion cells (RGCs) [28], are highly sensitive to blue light and they directly communicate with the brain [29], including the hippocampus [30]. Even more importantly, these RGCs contain Piezo2 and Piezo1, not to mention their role in RGCs damage [31]. Hence, the integration of the eye-brain axis and the microbiota-gut-brain axis through the hippocampal hub would explain the so-called gut-eye axis. Visible light is synchronized to our inner clock of the suprachiasmatic nuclei of the hypothalamus within the daily 24-hour cycle [29]. However, the short wavelength blue light, out of the visible light spectrum, is the strongest contribution to circadian system synchronization [29]. Important finding that one study showed on healthy youngsters that 30 minutes exposure to blue light one hour prior to bedtime had the impact of 30 minutes phase shift delay on the onset of REM sleep [32]. Noteworthy that the Piezo2 initiated ultrafast proton-based cross-frequency coupled oscillatory synchronizational signaling mechanism at the ultradian domain of circadian regulation through the gut-brain axis proposed to modulate REM sleep [9].

Accordingly, the author of this paper does not find accidental that the blue light exposure prior to sleeping has detrimental effect on the circadian system [29]. Therefore, the rapidly increasing exposure to blue light emitting devices right before sleep in the past two decades may also contribute to the degradation of the gut-eye axis and increased incidence of ∞ CRC.

5. Concluding Remarks

The current opinion manuscript 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 ∞ 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 onset, hence not only contributes to cancer initiation, lost circadian rhythms, but later to proliferation and metastasis as well.

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