



# Cystic Fibrosis Transmembrane Regulator and Risk of Gastrointestinal Cancer

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## Editorial

The risk of Gastrointestinal (GI) cancers in patients with Cystic Fibrosis (CF) is high, and such a risk is not always fully taken into consideration, as Yamada et al. [1]. CF is characterized by altered management of intracellular Chloride (Cl<sup>-</sup>), owing to altered sequences in the Cystic Fibrosis Transmembrane Regulator gene (CFTR). The heterozygous frequency of at least one of the over 1900 mutated sequences of this gene occurs in one of 13 and one of 24 people, respectively, of Ashkenazy and of European descent, a non- infrequent occurrence. Altered Cl<sup>-</sup> transport might occur also in heterozygous individuals, albeit at a somewhat non-dangerous level. Additional increased modification of Cl<sup>-</sup> transport can be caused by the Vacuolating Toxin (VacA) of *Helicobacter pylori* as its p33 subunit with the N-terminal part of the p55 subunit also acts as a chloride channel [2]. VacA is known to circulate in vesicles called exosomes; these are very stable, can enter any cell type, and, therefore, have been proposed as a vehicle for therapies that need to reach distant organs. We wish to report our experience of testing chloride (Cl<sup>-</sup>) concentration in the sweat of patients with liver cirrhosis, aiming at excluding a risk factor for liver cancer development. Cl<sup>-</sup> levels above 59 mmol/L were found in 13 adult female patients who accepted to perform the test at the Regional Centre for cystic fibrosis of Torino; this level is a bona fide positive for Cystic Fibrosis Transmembrane Regulator (CFTR) dysregulation. Seven of these patients had already been diagnosed with cancer (or subsequently were diagnosed) at varying sites (two in breast, one each lung, liver, endometrium, stomach, acoustic nerve). This finding was unexpected, and troublesome; however it follows the laws of thermodynamics. Indeed, Cl<sup>-</sup> contributes to the transmembrane voltage (V<sub>mem</sub>), which in turn controls cell proliferation [3]. Chernet et al. [4] demonstrated that control of Cl<sup>-</sup> concentrations in the medium can stop cancer. Lucia et al. [5] showed that ion management, of Cl<sup>-</sup> in particular, requires very high quantity of energy: Cl<sup>-</sup> entry in cells provides large amount of energy that can be spent for growth. Lastly, it was shown that blockade of Cl<sup>-</sup> channel enhances apoptosis of chemotherapeutic drug-resistant cancer stem cells [6]. We and others found that most patients with Hepatocellular Carcinoma (HCC) are also infected by *H.pylori*; possibly also its Cl<sup>-</sup> transport modifying activity might be involved in HCC development [7-10]. We believe it is necessary to raise awareness on cancer related risk of mutated CFTR, and on the Cl<sup>-</sup> transport modifying capabilities of VacA. We wish to further study Cl<sup>-</sup> concentration in sweat, a non-invasive and rather inexpensive test; hopefully, it could help in the prevention of at least some GI cancers.

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