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THE ROLE OF CYSTIC FIBROSIS TRANSMEMBRANE REGULATOR IN CELL MIGRATION

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Introduction: Cystic Fibrosis (CF) is a genetic disorder that damages the lungs and digestive system due to disrupted salt and water transport across epithelium. Patients with CF are now living longer as a result of improved treatments that reduce the symptoms of thick mucus and blocked secretion of digestive enzymes. Unfortunately, as individuals with CF age, they are at increased risk of other diseases, such as colon cancer. Colon cancer is 4 to 8 times more likely to develop in patients with CF than the general population. The risk of colon cancer is 11 times higher for CF patients with a history of distal intestinal obstruction syndrome and increases to over 30 times higher for patients who have received a solid organ transplant.
Methods: To determine if the elevated incidence of colon cancer in CF patients is due to defective cystic fibrosis transmembrane conductance regulator (CFTR) function, a scratch assay was performed on cultured human colon cells. The scratch was imaged every 24 hours for five days. Wound area and cell migration were measured in the presence of 5 µM Forskolin and 500 µM IBMX (a CFTR activator) or 5 µM CFTR (inh)- 172 (a CFTR inhibitor).
Results: Control and CFTR inhibitor treated cells grew to fill in the wound area by day 3 with an average migration of 55.38 ±14.74 and 63.94 ±7.39 μm^2/24 hours respectively. The CFTR activator treatment group did not completely grow into the space by this time with an average migration of 27.45±1.31 μm^2/24 hours and about 70% of the wound area still open on the third day. The cystic fibrosis transmembrane conductance regulator plays an important role in the rate of cell migration and thus cancer progression.

Figure 1.

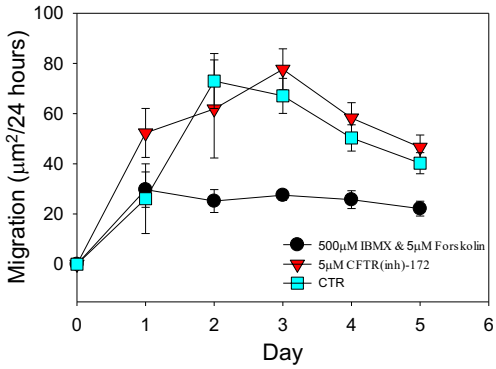

Figure 1. Activated CFTR decreases cell migration**.** Cells treated with CFTR activators [Forskolin (5 µM) and IBMX (500 µM)] had an average migration rate of 26.05 ± 1.25μm^2/24 hours. The control and inhibited CFTR cells had migration rates of 51.34 ± 8.5μm^2/24 hours and 59.33 ± 5.26μm^2/24 hours respectively. *= $p<0.05$

Figure 2.

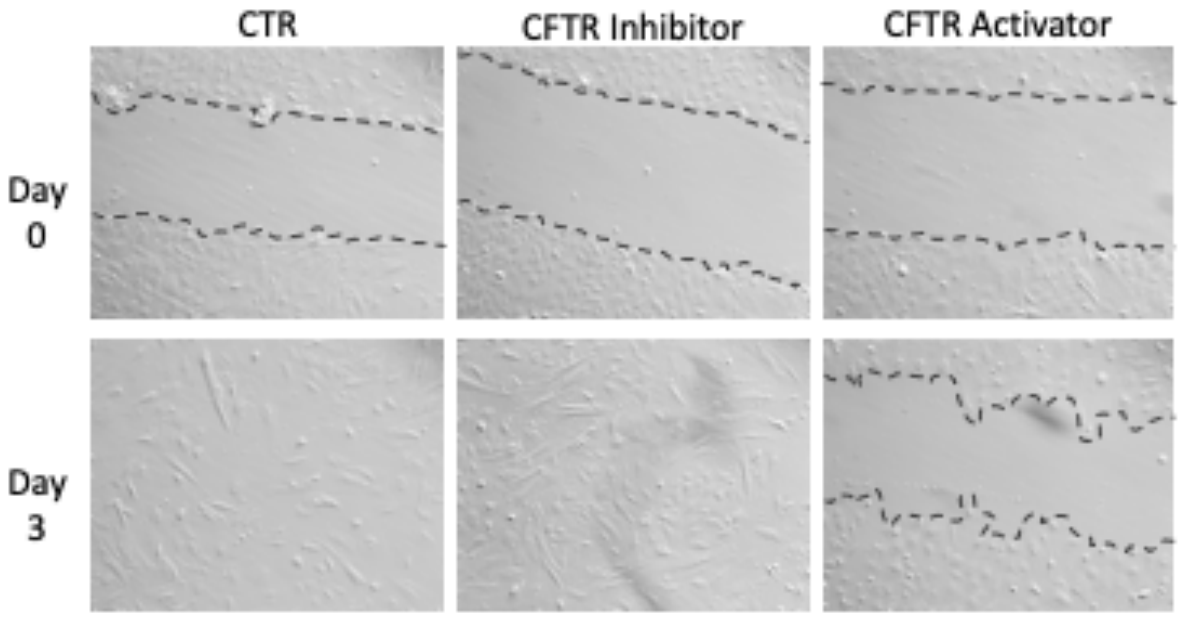

Figure 2. Activation of CFTR significantly attenuates wound closure. Representative scratch areas shown on days 0 and 3 in CTR, CFTR inhibited, and CFTR activated colon cells.

Figure 3.

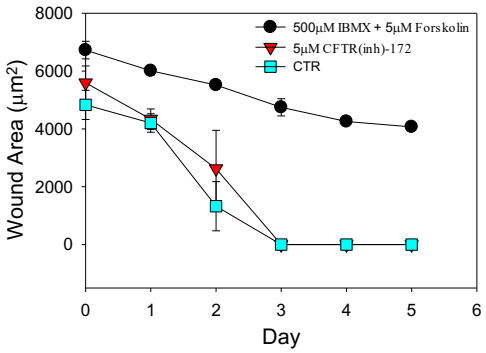

Figure 3. Wound area is inversely related to cell migration. (See Figure 1) *= $p<0.05$

Figure 4.

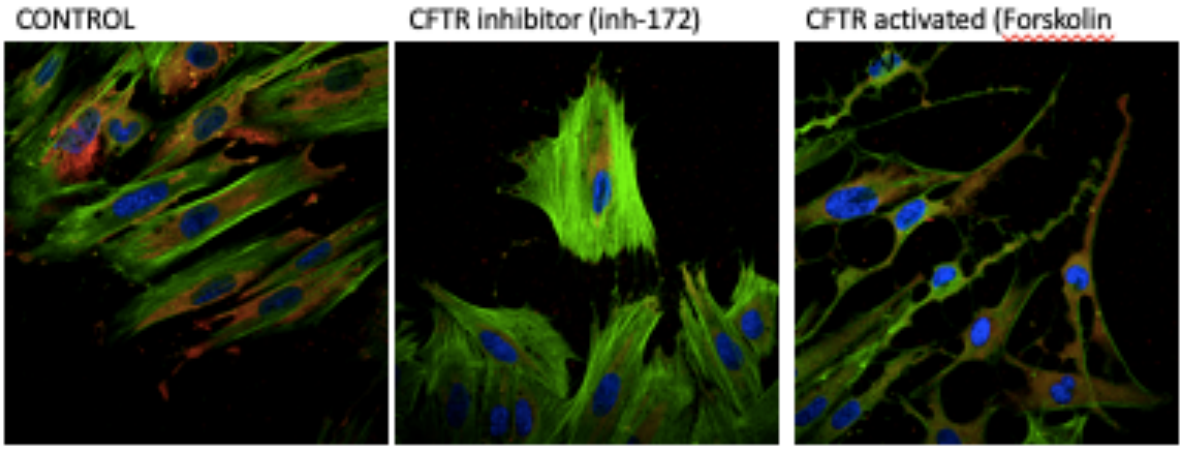

Figure 4. Human colon epithelial cells co-labeled with anti-CFTR antibody (conjugated to Alexa Red) and anti-epidermal growth factor receptor (EGFR; conjugated to GFP) 24 hrs post scratch. Inhibition of CFTR significantly alters cellular localization of EGFR vs. Forskolin and IBMX treated cells. This suggests that EGFR plays a role in cell migration.

Conclusion:

Loss of cystic fibrosis transmembrane conductance regulator (in CF patients) leads to increased epidermal growth factor receptor mediated cell migration (cancer progression).