427r Chemotaxis Machinery of Salmonella Typhimurium Controls Its Accumulation in Tumors

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Multi-drug resistance greatly limits the efficacy of conventional blood-borne chemotherapeutics which have limited ability to penetrate through tumor interstitum and are ineffective at killing quiescent cells far from tumor vasculature. Nonpathogenic, motile Salmonella typhimurium, which are specifically attracted to compounds released by quiescent cells, are an alternative to overcome many of the diffusion and convection limitations encountered by standard treatments. Using cylindroids, we test the hypothesis that the chemotaxis machinery of S. typhimurium controls its accumulation in solid tumors. We have used a series of S. typhimurium strains that lack either one of the major chemotaxis receptors or part of the chemotaxis signal transduction pathway, to determine the controlling mechanism of S. typhimurium accumulation in tumors. Each strain was transfected with GFP and the ability to chemotaxis towards specific attractants was quantified using the capillary assay. Accumulation in tumors was measured using the cylindroid in vitro tumor model, time-lapse fluorescence microscopy, and specifically designed image and mathematical analysis techniques. Using the capillary assay we have confirmed that knockout strains do not chemotax to their respective ligands (i.e. tsr toward serine), but retain attraction to other ligands. Strains lacking part of the signal transduction pathway were unable to chemotaxis or accumulate within tumor cylindroids. S. typhimurium lacking the transmembrane chemoreceptors for serine was able to chemotax towards, but not accumulate within tumor cylindroids. However, those S. typhimurium lacking one of the minor transmembrane chemoreceptors, ribose and galactose or citrate, was able to chemotax and accumulate in tumors cylindroids similar to the wild-type strain. Understanding the mechanism of S. typhimurium preferential growth and chemotaxis in tumor cylindroids has great implications for developing and improving bacteriolytic therapies; genetically manipulated strains of S. typhimurium can be engineered to homogeneously accumulate and proliferate in inaccessible tumor regions in vivo.