Multiscale models of tumor growth with explicit receptor-ligand dynamics to quantify tumorigenesis conditions

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Abstract

Ligand–receptor dynamics play a dominant role in tumorigenesis, proliferation, immunosuppression, and angiogenesis. Existing tumor models put little emphasis on explicit receptor–ligand interactions. We address this gap by elucidating the epidermal growth factor (EGF) and its receptor (EGFR) thresholds that initiate tumor growth under normal and pathological conditions through four complementary modeling frameworks. First, we refine a previously designed 3D multiscale model of tumorigenesis, incorporating EGF–EGFR interactions by calibrating it to physiological molecular levels and simplifying intracellular regulation for computational speed. Second, we introduce the first receptor-structured continuous model, parameterized directly from multiscale simulations. Both models are validated against *in vivo* data linking EGFR expression to tumor volume. We then construct surrogate machine learning meta-models and a reduced ODE version for the multiscale and continuous frameworks, respectively, to enable rapid parameter exploration and the derivation of analytical estimates. Across models, we identify numerical and theoretical thresholds of EGF and EGFR concentrations that enable tumor initiation and quantify them according to microenvironment conditions. The models show that the number of EGFRs required to initiate tumor growth depends solely on cell phenotypes. In contrast, the EGF concentration needed to promote tumorigenesis decreases with higher EGFR expression and lower EGF–EGFR unbinding constants. We conclude by discussing the strengths and limitations of the four models. These findings reveal fundamental thresholds in receptor–ligand dynamics, which could inform strategies to optimize targeted cancer therapies.