Analysis of Ras as a tumor suppressor

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***Short Abstract* — Oncogenic Ras mutations are common drivers of human cancer. One poorly understood aspect of Ras biology is the apparent tumor suppressor activity that wild-type Ras sometimes appears to exhibit. This problem was investigated with a computational model of Ras signaling. Modeling demonstrates that tumor suppressor activity is actually not needed to explain data commonly interpreted to support the tumor suppressor argument. Modeling also finds that small changes in oncogene expression after the loss of the wild-type allele would have an effect that could be interpreted as the wild-type allele having acted as a tumor suppressor.**

***Keywords* — oncogene, tumor suppressor, Ras, cell signaling**

I. Introduction

MUTATIONS to the Ras GTPases are among the most common cancer promoting mutations [1]. It is now understood that oncogenic Ras mutations lead to constitutive proliferative signals [2]. Still unexplained is the tumor suppressor behavior that the Ras proto-oncogene sometimes appears to demonstrate [3-7].

A mathematical model of Ras signaling that accounts for the multiple biochemical mechanisms that regulate Ras activity has previously been developed and applied to the study of cancer promoting Ras mutations [8,9] and Ras pathway mutations [10]. The model allows one to find the behaviors that logically follow from what is already known and quantified about Ras biology. Here, the model is applied to the problem of whether or not wild-type (WT) Ras has "tumor suppressor" properties.

II. Results

Arguments that Ras has tumor suppressor activity commonly refer to the frequent loss of heterozygosity (LOH) in Ras genes when a Ras oncogenic mutant is present. Common mechanisms for LOH not only result in a loss of the WT allele, but also in the duplication of the mutant allele [3,5]. Simulations find that doubling mutant expression results in a large increase in Ras signaling. This modeling result is consistent with experimental data that examines the consequences of Ras mutant dosage [6]. This suggests that tumor suppressor activity is not necessary to explain the LOH data.

Arguments that Ras has tumor suppressor activity also refer to the inhibition of mutant Ras signals by dominant negative (DN) Ras mutants [5]. However, model simulations find DN Ras results in less oncogenic Ras signaling. This follows from the inhibition of Ras GEFs by DN Ras. This suggests that tumor suppressor activity is not needed to explain DN Ras data.

A compelling argument for tumor suppressor activity comes from mouse studies [4]. In these studies, *Kras* mutations were chemically induced. Mice with only one wild-type allele ($Kras^{+/-}$) developed more tumors than mice with two wild-type alleles ($Kras^{+/+}$). Our simulations suggest that *Kras* mutants would generate a higher level of Ras signal in the +/- mice if the +/- mice express more than 50% as much KRas protein as the +/+ mice. The exact amount of expression varies based on the concentrations of Ras network proteins, but ranges from as low as 51% to as much as 65% of the amount of KRas expressed in the $Kras^{+/+}$ mice. Experiments quantifying protein expression in these studies have typically been used to demonstrate less KRas in the +/- mouse, not to precisely quantify how much less KRas is in the +/- mouse.

III. Conclusion

Our analysis finds much of the data used to argue that WT Ras has tumor suppressor activity is actually consistent with the well-established activity of mutant Ras. Our simulations also suggest that a low level of increased expression from a single Ras allele could explain the increased tumor burdens in $Kras^{+/-}$ mice compared to $Kras^{+/+}$ mice. Quantitative measurements of Ras protein expression that are capable of detecting small changes in expression could distinguish our hypothesis from the tumor suppressor hypothesis. Overall, this study demonstrates how quantitative modeling can contribute to the study of unresolved problems in cancer biology.

References

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