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Escape from Tumor Dormancy Following Gene- Or Viro- therapies is Mediated by Acquisition of a Phenotype in which Innate Immune Surveillance Actively Drives Tumor Cell Recurrence.

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When established (~0.3-0.5cm) primary murine B16 tumors are treated with either cytotoxic gene therapy (HSVtk/GCV), oncolytic virotherapy (intra-tumoral reovirus) or adoptive T cell therapy, a proportion of mice will become apparently tumor free. However, if the animals are observed for prolonged periods of time (>60-100 days), the majority of mice will develop aggressively growing recurrent tumors. Excision of the site of tumor injection during the period of tumor dormancy (no palpable tumor) indicated that residual tumor cells are readily detectable in most mice by histology. Unexpectedly, it was extremely difficult to re-grow the tumor cells from these specks of minimal residual disease *in vitro*. However, by screening multiple cytokines for their ability to support re-growth of recurrent B16 cells, we identified TNF-α as a major growth factor for recurrent cells. Conversely, treatment of primary B16 populations with TNF-α led to highly significant reductions in tumor cell viability. Similarly, depletion of NK cells, or antibody blockade of TNF-α, from C57Bl/6 mice led to significantly increased tumorigencity of primary B16 tumors. In contrast, depletion of NK cells allowed for decreased tumorigenicity of TNF-α stimulated recurrent B16 cells recovered from mice in a state of minimal residual disease. These data suggest that tumor recurrence may be mediated by a distinct phenotypic switch *in vivo*. Thus, initially, primary tumor cells are highly sensitive to innate immune cell surveillance through NK cells and TNF-α. However, escape from dormancy in vivo is associated with acquisition of a phenotype in which such TNF-α-mediated immune surveillance actively drives tumor growth. TNF-α growth promoted recurrent cells also expressed high levels of PD-L1 compared to primary tumor cells, suggesting that this may be a further mechanism by which recurrences could emerge *in vivo*, even in the presence of anti tumor T cell responses. Consistent with this hypothesis, recurrence was significantly inhibited *in vivo* following gene, viro- or adoptive T cell therapies, by treatment with TNF-α blockade or systemic checkpoint inhibitor therapy.