

True Immunogenicity of Oncofetal Antigen/Immature Laminin Receptor Protein

To the Editor: Su *et al.* (1) described the detection of RNA present in renal cell carcinoma (RCC) that achieved expression of oncofetal antigen (OFA) in RCC patient's monocytes and gave rise to OFA-expressing dendritic cells *ex vivo*. When these OFA-expressing dendritic cells were infused back into autologous patients with metastatic RCC, OFA served as a distinct tumor-associated rejection antigen, as did telomerase reverse transcriptase and G250, which were also expressed on some RCC tumors. Whereas this observation is interesting, we disagree on the following points.

1. The designation of OFA as a nonimmunogenic, overexpressed "self-protein" based on the RNA data presented lacked adequate consideration of the effects of posttranslational modification (acylation) and dimerization with β -galactin on the immunogenicity to the mature form of the molecule encoded by the mRNA examined in adult, normal cells (2, 3). This made the interpretation of data presented unnecessarily confusing. It is critical to recognize that OFA or immature laminin receptor protein (OFA/iLRP) is, in fact, the tumor-specific, auto-immunogenic protein when expressed as a 37-kDa, nonacylated, monomeric protein in association with tumor cell plasma membranes that activated several subclasses (Tc, Ts, and Th1) and B cells inducing antitumor antibody in mice and humans (2–8). In contrast, 67-kDa mature laminin receptor is the nonimmunogenic self-antigen referred to in the report. Pre-T cells capable of responding to mature laminin receptor are presumably deleted at thymic maturation in human and mice.

2. The omission of other prior reports clarifying host OFA/iLRP immunogenicity in renal cancer (9, 10) and other cancer types (4–8) may have resulted in serious misconceptions about OFA/iLRP as a tumor-specific rejection antigen for stimulating host T-cell clones.

3. The incorrect citation of other work (11) by Su *et al.* (1) was stated to relate to OFA's specific characterization as a tumor rejection immunogen in rodents and humans. Unfortunately, this reference (11) does not address these issues, whereas other reports presenting these data were not considered (2–10).

4. The statement in this report (1) that "G250 and hTERT (human telomerase reverse transcriptase) were the only TAAs (tumor-associated antigens) that could be detected in all of the renal tumors but not in the corresponding benign renal tissues, whereas OFA demonstrated high expression in both tissue types examined at the RNA level" is absolutely contradicted by findings that the 37-kDa OFA/iLRP was a T-cell immunogen in mouse tumor models (5–7) and in human breast (7, 8) and RCC patients (9, 10).

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In Response: We agree and are aware of Dr. Coggin's statements on oncofetal antigen immunogenicity; however, his criticisms are based on major misconceptions regarding the vaccine approach used in our study (1) and do not relate to our stated objectives and conclusions. As clearly shown in the title and text of our publication (1), renal tumor RNA-transfected dendritic cells and not oncofetal antigen mRNA-transfected dendritic cells were used for vaccination and stimulated T-cell responses that, in part, contained reactivities against oncofetal antigen, telomerase (human telomerase reverse transcriptase), and G250. Oncofetal antigen mRNA-transfected dendritic cells were not used to immunize patients or to stimulate T-cell responses *in vitro* but were merely used as surrogate targets in IFN- γ ELISPOT assays to determine antigen-specific T-cell frequencies contained in the vaccine-induced, tumor-specific T-cell response. In the same manner, telomerase (human telomerase reverse transcriptase)- and G250 mRNA-transfected dendritic cells were also used as surrogate targets without further expanding on the biology or immunology of these self-antigens. It was never our intent to provide quantitative comparisons on the immunogenicity of each antigen, but rather to provide evidence on the polyclonality of the vaccine-induced T-cell response suggested in prior studies performed by our group.

Thank you for the opportunity to respond to Dr. Coggin's letter.

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