Neonatal Fc receptors for IgG drive CD8+ T cell-mediated anti-cancer immunosurveillance at tolerogenic mucosal sites

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Cancers arise with a disproportionately high frequency in tissues of mucosal origin such as the lung, stomach, and colon.1 One important contributor to the increased risk of neoplasia at these sites is the immunosuppressive nature of the mucosal immune system. While this is required for the tolerance of innocuous foreign oral and airborne antigens (be them of microbial or non-microbial origin), but generates an ideal environment for neoplastic growth to proceed under controlled conditions in which low amounts of TAAs are available.7 With respect to self antigens, natural auto-antibodies against widely expressed molecules such as phosphatidylserine are expected to be critical for the initial delivery of TAAs, alone or as part of exosomes or apoptotic bodies, to the FcRn-dependent processing pathway.8 Subsequently, the release of additional TAAs from rapidly dying cancer cells might increase the amount of local IgG-containing ICs and thus strengthen homeostatic tumor-protective immune responses and the immune system, in conditions in which low amounts of TAAs are available.9 The expression of FcRn by DCs of mesenteric lymph nodes and the lamina propria of untreated, healthy mice is critical for the establishment of homeostatic tumor-protective immune responses in the large intestine (LI), since the LI of FcRn deficient mice contains reduced numbers of CD8+ T cells, T1-polarized CD4+ T cells and transcripts coding for T1 cytokines.16 Not only do these studies demonstrate a physiological role for the FcRn in integrating B-cell and T-cell immunity as it regulates the fate of internalized IgG-containing ICs but also show for the first time that FcRn is able to orchestrate an intracellular signaling cascade when cross-linked by ICs.

Importantly, the high concentration of IgGs present at mucosal tissues is a critical prerequisite for FcRn-mediated immunosurveillance. While the exact specificity of such IgGs remains unknown, it can be speculated that the mucosal IgG repertoire will be reactive against both commensal microorganisms and self antigens. Although FcRn deficiency does not alter the composition of the LI microbiota, a contribution of the local microflora to FcRn-mediated immunosurveillance cannot be formally excluded.7 With respect to self antigens, natural auto-antibodies against widely expressed molecules such as phosphatidylserine are expected to be critical for the initial delivery of TAAs, alone or as part of exosomes or apoptotic bodies, to the FcRn-dependent processing pathways.8 Subsequently, the release of additional TAAs from rapidly dying cancer cells might increase the amount of local IgG-containing ICs and thus strengthen the magnitude of this response.9

Mucosal boundaries, which are immunologically tolerogenic, undergo malignant transformation at high rates. We have identified the expression of neonatal Fc receptor for IgG (FcRn) by dendritic cells as a critical mediator of mucosal anti-cancer immunosurveillance. This discovery extends our understanding of neonatal Fc receptors, defines a role for tumor-specific CD8+ T cells, and identifies an avenue for the development of novel anti-cancer therapeutics.

**Keywords:** FcRn, IgG, colorectal cancer, mucosal immunology, inflammation, dendritic cells
Our findings shed new light on the FcRn for the development of novel therapies to target established tumors. Indeed, targeting the FcRn-dependent antigen processing pathway of DCs, which can override the tolerogenic mucosal milieu, is a promising strategy for circumventing the robust state of immunosuppression that is orchestrated by malignant cells in the tumor microenvironment. Exploiting the FcRn biology using IgGs of known specificity is extremely feasible, given that at least one known mutation in the Fc enhances FcRn-dependent antigen presentation. Furthermore, it is possible that the efficacy of blocking antibodies such as trastuzumab, a v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2)-targeting molecule currently used to treat breast cancer patients, results (at least in part) from the formation of IgG-containing ICs that are delivered to the FcRn-dependent antigen processing pathways of DCs, enabling the generation of robust CD8+ T-cell response.

FcRn-mediated tumor immunosurveillance results from the integration of the humoral and cellular branches of immunity, the translation of specific antibody responses into targeted CD8+ T-cell responses and, ultimately, the breakdown of local tolerance to oncogenesis. Therapeutically manipulating this robust mechanism of immunosurveillance in appropriate models will further improve our understanding of the immunological functions of FcRn within mucosal tissues.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

References


