Cancer Cell
Article

FcRγ Activation Regulates Inflammation-Associated Squamous Carcinogenesis

Pauline Andreu,[1,5] Magnus Johansson,[1,5] Nesrine I. Affara,[1,5] Ferdinando Pucci,[3] Tingting Tan,[1] Simon Junankar,[1] Lidiya Korets,[1] Julia Lam,[1] David Tawfik,[1] David G. DeNardo,[1] Luigi Naldini,[3] Karin E. de Visser,[4] Michele De Palma,[3] and Lisa M. Coussens[1,2,*]

[1]Department of Pathology
[2]Helen Diller Family Comprehensive Cancer Center
University of California, San Francisco, San Francisco, CA 94143, USA
[3]Angiogenesis and Tumor Targeting Research Unit, San Raffaele-Telethon Institute for Gene Therapy and Vita-Salute San Raffaele University, San Raffaele Institute, Milan, 20132, Italy
[4]Division of Molecular Biology, The Netherlands Cancer Institute, Amsterdam, 1066 CX, the Netherlands
[5]These authors contributed equally to this work
*Correspondence: lisa.coussens@ucsf.edu
DOI 10.1016/j.ccr.2009.12.019

SUMMARY

Chronically activated leukocytes recruited to premalignant tissues functionally contribute to cancer development; however, mechanisms underlying pro- versus anti-tumor programming of neoplastic tissues by immune cells remain obscure. Using the K14-HPV16 mouse model of squamous carcinogenesis, we report that B cells and humoral immunity foster cancer development by activating Fcγ receptors (FcγRs) on resident and recruited myeloid cells. Stromal accumulation of autoantibodies in premalignant skin, through their interaction with activating FcγRs, regulate recruitment, composition, and bioeffector functions of leukocytes in neoplastic tissue, which in turn promote neoplastic progression and subsequent carcinoma development. These findings support a model in which B cells, humoral immunity, and activating FcγRs are required for establishing chronic inflammatory programs that promote de novo carcinogenesis.

INTRODUCTION

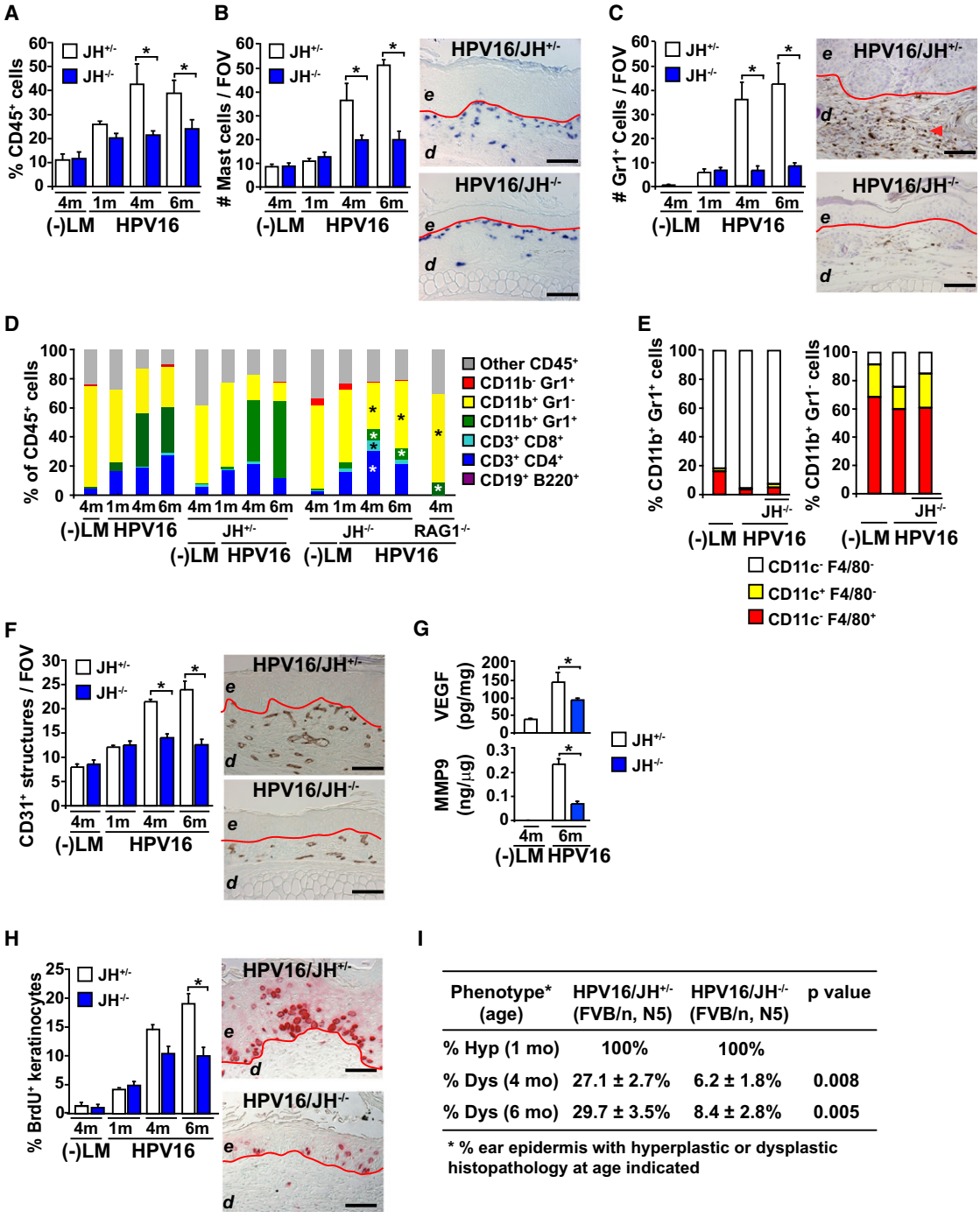
Clinical, epidemiological, and experimental studies have established that chronic inflammation contributes to various aspects of solid tumor development (de Visser et al., 2006; Mantovani et al., 2008). In particular, chronic inflammatory diseases, including several autoimmune disorders, are associated with increased risk of cancer development (Brandtzaeg et al., 2006; Dalgleish and O'Byrne, 2002), revealing that B cell hyperactivity combined with altered cellular immunity cooperate to initiate and/or sustain persistent inflammation that enhances overall cancer risk in afflicted tissues.

Deposition of B lymphocyte-derived immunoglobulins (Igs) is a common occurrence in premalignant and malignant stroma of human cancers (de Visser et al., 2006; Tan and Coussens, 2007). In addition, high levels of circulating immune complexes (CIC) are associated with increased tumor burden and poor prognosis in patients with breast, genitourinary, and head and neck malignancies (Tan and Coussens, 2007). While little is known about the function of CICs in tumor development, the role of CICs in inflammatory and autoimmune diseases is undisputed. CIC deposition in stroma has been implicated as an initiator of inflammatory cascades by mechanisms that include activation of complement pathways and engagement of the receptors for the crystallizable region (Fc) of IgG (FcγRs) on the surface of leukocytes (Takai, 2005). As such, FcγRs represent a functional link between adaptive and innate immunity by coupling interactions between circulating (auto)antibodies and innate immune cells (Nimmerjahn and Ravetch, 2008).

Four classes of IgG receptor FcγRs have been identified, FcγRI/CD64, FcγRII/CD32, FcγRIII/CD16, and FcγRIV, differing by their distinct affinity for IgG isotypes, cellular distributions, and effector functions (Nimmerjahn and Ravetch, 2008). Activating types of FcγRs form multimeric complexes including the

Significance

Andreu and colleagues demonstrate that peripheral activation of humoral immunity and subsequent activation of FcγRs on myeloid cells regulate critical features of carcinogenesis that foster solid tumor development. This work reveals previously unrecognized targets for therapeutic intervention in solid tumors, namely, B cells and FcRγ-signaling pathways that work in concert to differentially regulate not only the composition of leukocytes recruited to premalignant tissues but also their bioeffector functions once present.



Phenotype* (age)	HPV16/JH$^{+/-}$ (FVB/n, N5)	HPV16/JH$^{-/-}$ (FVB/n, N5)	p value
% Hyp (1 mo)	100%	100%	
% Dys (4 mo)	27.1 ± 2.7%	6.2 ± 1.8%	0.008
% Dys (6 mo)	29.7 ± 3.5%	8.4 ± 2.8%	0.005

* % ear epidermis with hyperplastic or dysplastic histopathology at age indicated

Figure 1. B Cells Are Critical Regulators of Premalignant Progression in HPV16 Mice

(A) Percentage of CD45$^+$ cells in skin single cell suspensions isolated from negative littermates (−LM), HPV16/JH$^{+/-}$, and HPV16/JH$^{-/-}$ mice at 1, 4, and 6 months of age assessed by flow cytometry.

(B and C) Mast cells (B, blue staining) and Gr1$^+$ myeloid cells (C, brown staining) in skin of HPV16/JH$^{+/-}$ and HPV16/JH$^{-/-}$ mice at 1, 4, and 6 months of age assessed quantitatively after chloroacetate esterase histochemistry or Gr1 immunohistochemistry (IHC), respectively.

(D) Flow cytometric analysis of immune cell lineages expressed as percentages of total CD45$^+$ leukocyte infiltrates in ear tissue of negative littermates (−LM), HPV16, HPV16/JH$^{+/-}$, HPV16/JH$^{-/-}$, and HPV16/RAG1$^{-/-}$ mice at 1, 4, and 6 months of age.

(E) Dendritic (CD11c$^+$) and macrophage (F4/80$^+$) lineage cell composition of CD11b$^+$Gr1$^+$ (left) and CD11b$^+$Gr1$^-$ (right) myeloid populations evaluated by flow cytometry in skin of negative littermates (−LM), HPV16, and HPV16/JH$^{-/-}$ mice at 4 months of age.

(F) Angiogenic vasculature in skin tissue sections from negative littermates (−LM), HPV16/JH$^{+/-}$, and HPV16/JH$^{-/-}$ mice at 1, 4, and 6 months of evaluation by CD31/PECAM-1 IHC revealing endothelial cells (brown staining).

(G) Reduced VEGF-A and active MMP-9 protein levels in skin extracts from HPV16/JH$^{-/-}$ versus HPV16/JH$^{+/-}$ mice (4 and 6 months) as assessed by ELISA.