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Current Opinion in Virology

Human papillomavirus infection and induction of neoplasia: a matter of fitness

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The aetiologic association between infection with certain human papillomavirus (HPV) types, high-grade squamous neoplasia, and cancer at different epithelial sites is well established. In this review we briefly discuss recent breakthroughs in the regulation of squamous epithelia in homeostasis and disease, and provide a view of how these discoveries modify our understanding of how HPV-induced neoplasia in squamous epithelia is triggered. Taken together, these observations highlight how HPVs have evolved the ability to inactivate the products of genes that are frequently mutated in non-HPV-associated pre-neoplasia and squamous cell carcinoma of sun-exposed skin, and introduce a Darwinian model of clonal evolution of HPV-infected cells. These concepts are considered against our current understanding of transformation zones where HPV-associated cancers occur more frequently, and other sites of non-productive (or abortive) HPV infection.

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Current Opinion in Virology 2016, **20**:xx–yy

This review comes from a themed issue on **Viruses and cancer**

Edited by **Ann Moorman** and **Christian Münz**

http://dx.doi.org/10.1016/j.coviro.2016.08.011

HPV infection, cell competition and clonal dominance

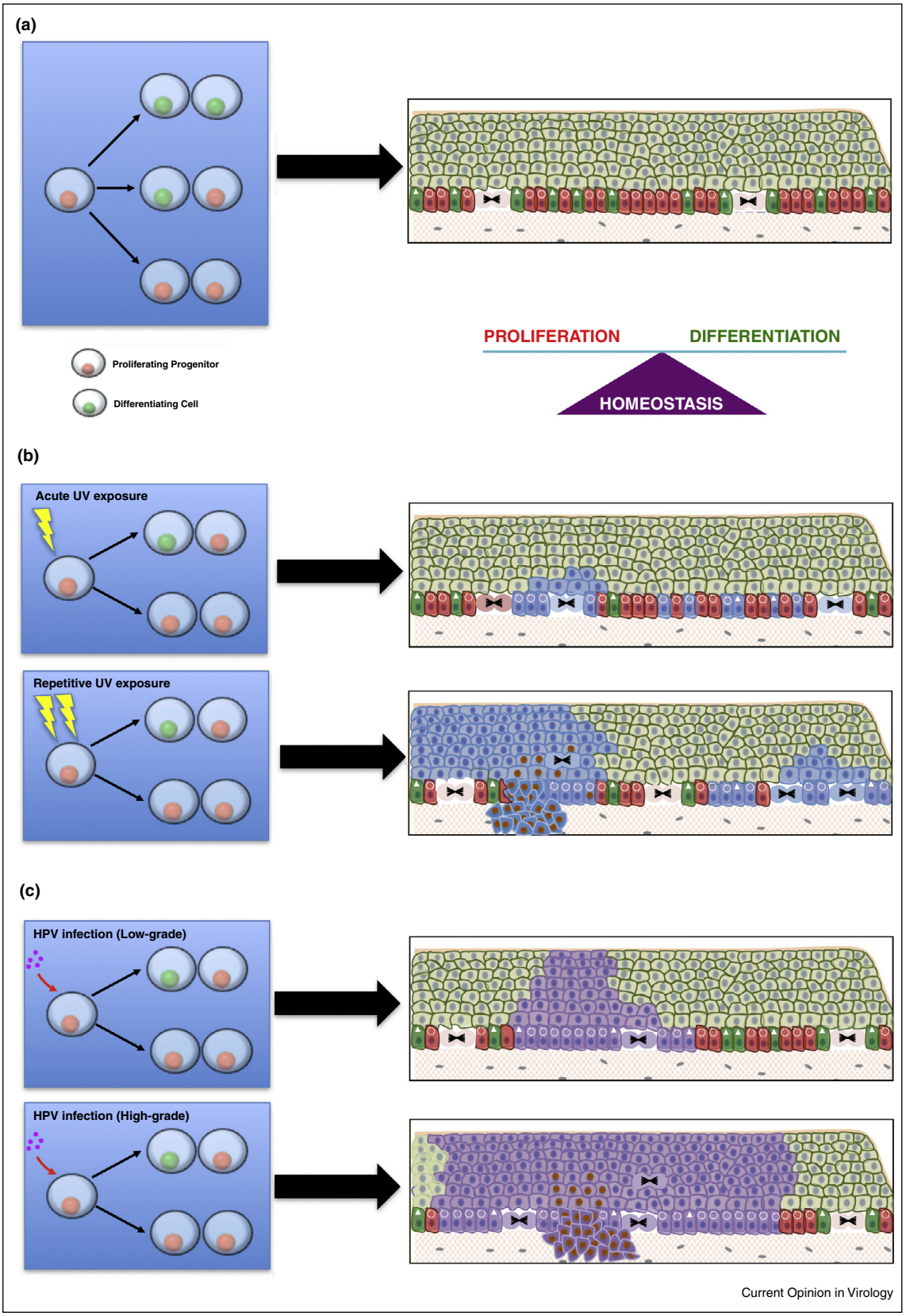
Current thinking suggests that Human Papillomavirus (HPV) infection, requires access to an epithelial 'stem cell' residing in the basal layer of a stratified epithelium [1–4]. In squamous epithelia this is thought to require a microwound, which exposes the basal lamina, allowing access of virus particles and subsequent virus entry [5]. In order to understand how viral gene expression can modulate normal epithelial function and cause disease, we need however to consider the dynamics of the various epithelial sites that HPVs infect.

In recent years, the advent of animal models and genetic approaches for the *in vivo* tracking of reporter genes (e.g. an enzyme or a fluorescent protein) in a subset of cells in adult tissues [6,7], has shed light on epithelial cell dynamics at different body sites during homeostasis and the development of disease [8]. In the squamous epithelia of mouse interfollicular epidermis and oesophagus, for instance, these types of studies are challenging the epidermal proliferative unit (EPU) and stem/transit amplifying (TA) cell hypotheses, which suggest that epithelial homeostasis is maintained by slow-cycling stem cells, that divide to generate cells with a limited proliferation potential primed to undergo terminal differentiation [9–11]. Recent studies using mouse models have ruled out the existence of 'true' stem cells in murine stratified interfollicular epithelia, but suggest instead, that homeostasis is maintained by a balance in the stochastic cell fate specification following cell division (modified by the local microenvironment and mutations), which can lead to three possible outcomes; that is, two proliferating cells, one proliferating and one differentiating cell or two differentiating cells (Figure 1a) [12–14]. By these means, the number of new proliferating cells always equals the number of cells lost by differentiation. Indeed, the squamous epithelium is a powerful self-regenerating and protective system, which ensures that cells lost through differentiation and shedding are replaced by 'fresh' progenitors, a process which also limits opportunities for the accumulation of oncogenic mutations. These emerging concepts should shape our thinking as to how epithelial cell dynamics may be modulated by HPV in the stratified epithelia, and how HPV-driven changes lead to the early manifestations of neoplasia.

During epithelial homeostasis, many genetic mutations that reduce the fitness of a cell compared to the wild-type population are eliminated through cell competition, a protective mechanism against tumorigenesis that has been observed *in vivo* [15,16]. On the other hand, a mutation that confers a competitive advantage on a cell in a given population (i.e. a driver mutation), has a higher chance to be selected for, persist long-term in the epithelium and undergo clonal expansion with an increased likelihood of accumulation of pro-oncogenic mutations (Figure 1b) [12,13,17]. This is the basis for the Darwinian model for clonal evolution of cancer [17–19], which well fits with the model of neoplastic progression of high-risk HPV infections. In the latter, lack of immune clearance and the persistent expression of viral gene products are major risk factors for the progression to high-grade neoplasia in the stratified epithelium (reviewed in [3,4]). To a large extent, the development of high-risk HPV-associated neoplasias

Please cite this article in press as: Kranjec C, Doorbar J: Human papillomavirus infection and induction of neoplasia: a matter of fitness, Curr Opin Virol (2016), http://dx.doi.org/10.1016/j.coviro.2016.08.011

Figure 1



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