Published in final edited form as:

Trends Immunol. 2015 September ; 36(9): 503–504. doi:10.1016/j.it.2015.07.008.

Do not scratch that mole!

Mark Jelcic¹ and Philipp Niethammer¹

¹Cell Biology Program, Memorial Sloan Kettering Cancer Center, 411 E 67th Street, New York, NY 10065

Abstract

Nevi harbor some of the same oncogene mutations that also drive malign melanoma. Further tumor promoting events are required to unleash their carcinogenic potential. Using zebrafish whose melanocytes overexpress an HRAS-oncogene, a new study reports that injury induces melanoma, possibly through recruitment of neutrophils that trigger proliferation of pre-neoplastic melanocytes.

Can repeated injury of a harmless mole turn it into a vicious cancer? While this is not typically considered a major medical concern, a recent zebrafish study [1] focusing on the notorious relationship between wounds and cancer seems to underline the principal plausibility of this unsettling idea.

Wounds share many phenotypic characteristics with tumors, including the increased expression of genes with oncogenic potential, the recruitment of immune cells, and increased epithelial cell migration and proliferation. This similarity is captured by a classic citation attributed to the German physician Rudolph Virchow, who described tumors as “wounds that do not heal.” Unlike wounds, tumors do not resolve because growth control pathways have been derailed by (epi-)genetic alterations. Thankfully, gain- or loss-of-function of a single cancer driver gene is typically not sufficient to lead to the derailment of normal cellular processes. Awakened the dangerous potential of slumbering oncogenes requires additional perturbations of cell fate, cell survival or genome maintenance pathways [2].

This “multiple hit” principle of carcinogenesis is reconciled by current zebrafish melanoma models. Owing to their small size and transparency, zebrafish larvae are an emerging research tool for studying tumor formation and metastasis by live imaging in the intact animal [3]. Mutated BRAF or NRAS proteins are two common drivers of human melanoma [2]. Zebrafish that express one of these oncogenes in their melanocytes develop nevi, but do not develop cancer unless genome maintenance mechanisms are inhibited by p53 deletion [4,5]. HRAS mutations are not frequent in human melanoma, but melanocytic expression of

Corresponding author: Niethammer, P. (niethamp@mskcc.org).

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

a HRASV12 oncogene sensitizes zebrafish for experimental melanoma, apparently even more effectively than sole expression of BRAF or NRAS mutants [6].

Using the HRASV12 melanoma model, Antonio *et al.* observed tumor formation at sites of the animal that are particularly prone to friction or damage, such as the ventral and tail fins where fish often happen to bite each other [1]. It has been known for a while that wounding can induce skin tumors. Mice that express a mutated oncogene or had been pretreated with a mutagenic chemical develop papilloma at the site of a skin injury. Likewise, wound-related melanoma formation in oncogene-sensitized mice has been previously reported [7].

Martin and colleagues tested whether injury and tumor development may be causally connected in their model, and found this to be the case. Of note, the Martin laboratory had previously demonstrated that HRAS12V expressing cells recruit nearby neutrophils through a redox dependent mechanism, and that that leukocytes promote proliferation of HRAS mutant cells through the release of trophic factors such as prostaglandin E2. In line with these earlier findings, Antonio *et al.* now show that wounding lures neutrophils into the “influence zone” of oncogene-expressing cells. The neutrophils nurture the oncogene-expressing melanocytes with trophic factors, including prostaglandin E2 [8]. Thus it seems conceivable that some of the tumor-promoting effects of a wound may derive from its ability to mediate long-range (including vascular) recruitment of many neutrophils to pre-neoplastic melanoma precursors. Consistent with a role for this process in the progression of human disease, ulceration and neutrophil (but not macrophage) infiltration were found to be correlated in patient melanoma samples [1].

How may neutrophil-mediated amplification of pre-neoplastic cells be related to tumor promotion? Clearly, the more often a cell divides, the more mutations it is likely to acquire, particularly when being exposed to high levels of DNA-damaging, antimicrobial factors, such as reactive oxygen species (ROS), which are abundant in inflammatory wound microenvironments. Thus, trophic factor exposure may increase the probability of HRASV12 cells acquiring additional driver mutations. Analogous mechanisms are thought to contribute to the pathogenesis of hormone-related cancers [9]. Yet, this answer is likely to be incomplete. Mere stimulation of cell proliferation is generally not sufficient to promote tumorigenesis in oncogene-sensitized animals. Albeit technically challenging, future experiments need to directly test whether the transition to malignant melanoma and subsequent disease progression depend on the presence of a trophic neutrophil sub-population. The possibility of such “neutrophil-addiction,” implied by the work of Antonio *et al.*, is truly intriguing.

These recent findings add to mounting evidence that a growth-supporting population of neutrophils exists. Earlier studies have indicated that neutrophils, like macrophages, are a very heterogeneous population. However, the prevailing paradigm still is that they are one-and-foremost professional killers that keep wounds pathogen-free. Neutrophil recruitment to wounds that contain few pathogens appears to impede rather than promote healing [10]. Likewise, sterile inflammatory neutrophil recruitment to damaged organs, e.g., after ischemia-reperfusion, holds no obvious benefit for the host. Quite on the contrary, neutrophil influx often produces surplus damage. It seems unlikely that neutrophils evolved

growth-promoting functions to help tumors. Whereas maladaptive, tumor-promoting behaviors are well established for macrophages, these can be more easily rationalized because a known, physiological function of macrophages is to support tissue healing and regeneration.

What could the physiological role of trophic neutrophils be? Although this is currently unclear, one can speculate: Many of the cytotoxic chemicals used by neutrophils to kill microbes, such as ROS, are unspecific toxins. This allows them to rapidly act against a wide range of unknown pathogens, but also renders damage to the host inevitable. Poisoning both pathogen and host cells (“N1”-functionality) while specifically improving the survivability of the host through trophic signals (“N2”-functionality), might be an adapted strategy of organisms to “retrospectively” enhance the selectivity of intrinsically unselective innate immune responses (Figure 1). Future work will be necessary to address this and other possibilities.

Finally, the broader implications of Antonio *et al.* warrant careful consideration, particularly in the context of cancer surgery, where wounds are unavoidable.

Acknowledgments

We would like to thank Richard White for helpful discussion. The authors are supported by the NIH grant GM099970, and the American Asthma Foundation Scholar Award AAF 14-0022 to P.N.

References

1. Antonio N, et al. The wound inflammatory response exacerbates growth of pre-neoplastic cells and progression to cancer. *EMBO J.* 2015;10.15252/embj.201490147
2. Vogelstein B, et al. Cancer genome landscapes. *Science.* 2013; 339:1546–58. [PubMed: 23539594]
3. White R, et al. Zebrafish cancer: the state of the art and the path forward. *Nat Rev Cancer.* 2013; 13:624–36. [PubMed: 23969693]
4. Patton EE, et al. BRAF mutations are sufficient to promote nevi formation and cooperate with p53 in the genesis of melanoma. *Curr Biol.* 2005; 15:249–254. [PubMed: 15694309]
5. Dovey M, et al. Oncogenic NRAS cooperates with p53 loss to generate melanoma in zebrafish. *Zebrafish.* 2009; 6:397–404. [PubMed: 19954345]
6. Santoriello C, et al. Kita driven expression of oncogenic HRAS leads to early onset and highly penetrant melanoma in zebrafish. *PLoS One.* 2010; 5:1–11.
7. Mintz B, Silvers WK. Transgenic mouse model of malignant skin melanoma. *Proc Natl Acad Sci U S A.* 1993; 90:8817–8821. [PubMed: 8415613]
8. Feng Y, et al. Live imaging of tumor initiation in zebrafish larvae reveals a trophic role for leukocyte-derived PGE2. *Curr Biol.* 2012; 22:1253–1259. [PubMed: 22658594]
9. Henderson BE, Feigelson HS. Hormonal carcinogenesis. *Carcinogenesis.* 2000; 21:427–433. [PubMed: 10688862]
10. Dovi JV, et al. Neutrophil function in the healing wound: Adding insult to injury? *Thromb Haemost.* 2004; 92:275–280. [PubMed: 15269822]

Figure 1.

Cartoon scheme depicting cytotoxic (N1, red) and trophic (N2, green) neutrophil functions in the context of the innate immune response to infection (right side), and tumor promotion (left side). The trophic activity of neutrophils in part compensates the collateral damage of an antimicrobial innate immune response (e.g., disinfection of wounds). In the absence of microbes or tissue damage, trophic functionality is prevailing, which stimulates (pre-)neoplastic cell proliferation.