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Short Communication

Normal Epithelial Cells have Defense Mechanisms against Cancer

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The number of new cases of cancer is 0.5 percent in men and women in the US [1]. This figure seems staggering at first. But given that our body has 50 trillion cells [2] and each cell could accumulate ~25 sporadic mutations in the genome per replication [3], we should realize that the cancer incidence is actually a lot less than what it could be. Furthermore, our cells are constantly exposed to carcinogens, mutagens, oxidative stress, UV radiation, etc. Then, why aren't we getting more cancers than what we actually get?

The answer is that our body is equipped with inherent defense mechanisms against cancer. These include immunosurveillance [4], DNA damage repair, cell death, senescence [5] and anti-oxidant mechanisms [6]. Besides, normal epithelial cells utilize additional protective mechanisms against malignancy. First, epithelial cells are surrounded by the basement membrane, the fibrous extracellular matrix (ECM) that filters out unwanted molecules, such as excessive growth factors and inflammatory cytokines [7]. Second, cells carrying "unfitted" mutations are eliminated by their surrounding "fitter" cells through a process termed "cell competition" [8]. Third, our laboratory previously reported that normal breast epithelial cells undergoing alveologenesis (i.e., mammary gland development during pregnancy) secrete a collection of factors that could selectively kill tumor cells, without affecting normal cells or subdue them into a dormant state [9,10]. These mechanisms become less efficient as we grow older, making cells more susceptible to a stress that could trigger cancer initiation.

In our laboratory, we are examining the possibility of an additional mechanism by which normal breast epithelial cells defend themselves against breast cancer. We hypothesize that nitric oxide (NO), produced by normal breast epithelial cells, biochemically modulates (i.e., S-nitrosylates) signalling and structural molecules within cells and microenvironment to help establish tissue homeostasis, while protecting tissues against tumorigenic stress. This hypothesis is based on our recent finding that normal breast epithelial cells produce a significant amount of NO in response to laminins, the major basement membrane proteins in the normal breast tissue. In contrast, this mechanism is compromised in malignant cells [11,12].

NO is a reactive gaseous signalling molecule ubiquitously expressed throughout our body. Although it is mainly studied in specialized tissues, including neurons, muscles, vasculatures and immune cells [13], it has been long known that NO is critically involved in many aspects of tissue morphogenesis in diverse organisms from invertebrates to rodents [14,15]. This is primarily due to NO's roles in promoting cell-cell junctions [16] and cell polarity [17] while inhibiting cell division and contractility mediated by RhoA kinase [18]. As for NO's role in cancer, there has been a widespread controversy over its biphasic (pro- and anti-tumor) roles [19-22] depending on the context and concentration [23]. As a result, the experimental data are conflicting so far [24,25]. We propose that normal breast tissues produce a basal level of NO to promote mammary morphogenesis and maintain tissue homeostasis. If the balance of this system is impaired, tumors will be initiated or cells will die.

One way by which NO mediates morphogenesis of normal breast tissues is that NO promotes formation of cell polarity and cell-cell junctions. This is done by NO's upregulation of cortical actin and E-cadherin junctions [11]. Such functions of NO are at least in part due to the localization of NO Synthase (NOS)-1 and -3 (neuronal and endothelial NOS, respectively) which are part of complexes involved in mechanotransduction of signals received at the ECM receptors [26,27]. In particular, NOS-1 interacts with the laminin receptor dystroglycan [27], while interacting with the polarity protein Scribble [17] which stabilizes E-cadherin junctions [28]. Upon NO production, proteins proximal to NOS (e.g., ECM receptors, ECM ligands, cytoskeletons, junction and polarity proteins as well as nuclear membrane proteins) are S-nitrosylated [29], which in turn modulates their functions to drive epithelial morphogenesis.

The second way is that NO upregulates the p53 pathway, through S-nitrosylation and inactivation of different p53 inhibitors, (e.g., MDM2 [30], HDAC [31] and Parkin [32,33]). Activated p53 in turn triggers a cascade of signalling events that ultimately elevates the biogenesis and stability of the basement membrane protein laminin [11]. Laminin is essential for the formation of the basement membrane anchored at hemidesmosome [12].

As an additional mechanism, we are currently examining the possibility that NO S-nitrosylates ECM proteins as well as growth factors sequestered at the ECM to regulate their functions for the maintenance of the normal breast tissues. In addition, we are analyzing the consequences of reduction of NO production, which disrupts mammary epithelial tissue structure and dysregulates the ECM components, ultimately leading to tumor initiation.

We are utilizing high-resolution and atomic force microscopy, rhometry, 3D organotypic co-culture of primary cells as well as animal models to test our hypotheses. We are also planning to profile S-nitrosylated proteins in normal vs. cancerous breast cells by biotin switch/mass spectrometry and test the relevance of this modification. We hope that completion of this project will fundamentally advance

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our understanding the self-defense mechanism of normal tissues and how this is destroyed under stress, exposing cells to tumorigenesis. Equally important, this project will at least in part clarify the role of NO in cancer and open up a new field of NO research.

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