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Role of Nitric Oxide (NO) in the Homeostasis of the Normal Breast and Relevance of its Loss to Stiffening of the Extracellular Matrix and Breast Tumor Initiation

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Editorial

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Editorial

Advances in technologies and screening have dramatically increased the incidence of breast cancer, with the staggering 30 percent increase during the past 30 years [1,2]. This increase is largely attributed to a remarkable 7 fold increase in the incidence of premalignant forms [3] that now account for over 25% of all breast cancers detected [4,5]. Premalignant forms are the direct precursors of invasive breast cancers [6], but are yet poorly understood [7]. While most changes in oncogenic gene expression occur during normal to premalignant progression [8], only a half the premalignant forms progress to invasive breast cancers, while the other half remain as benign lesions. However, there is no clear clue of how to distinguish those becoming invasive from the others that do not [7]. Such uncertainties contribute to the yet slow improvement in the treatment of the premalignant forms and, thus, breast cancer patients' survival [6]. Better understanding the etiology of premalignant forms (*tumor initiation* process) is a key to radically improving breast cancer treatment.

Despite yet immature understanding of the tumor initiation process, recent studies have unveiled that one of the major drivers of breast tumor initiation is the stiffer extracellular matrix (ECM). The ECM is a collection of substances secreted from cells serving as the structural and mechanical support of the tissue. In normal tissues, ECM regulates morphogenesis of the epithelia and homeostasis of the microenvironment while restraining tumorigenesis [9]. In premalignant and malignant lesions, however, the ECM has become stiffer [10], perturbing tissue structures and transforming cells [11]. ECM stiffening is caused by activation of fibrogenic signals, including TGFβ and collagen (COL) cross-linkers: lysyl oxidase (LOX) and tissue transglutaminase (tTG). These fibrogenic factors increase COL deposition through its higher biosynthesis, cross-linking and myofibroblast differentiation producing more COL [10]. However, it not fully understood what liberates these fibrogenic signals to induce tumor initiation, while they are subdued in normal tissues. Addressing this issue is critical to better understand the causes of ECM stiffening.

Our laboratory is testing our hypothesis that nitric oxide (NO) plays a key role in the homeostasis of the normal breast tissue, whereas reduction of NO liberates fibrogenic signals to induce breast tumor initiation. NO is a reactive gas produced by NO synthases (NOS 1-3) in response to stress and exerts pleiotropic functions in diverse tissues, especially in neurons, muscles, endothelia and immune cells [12]. NOS-1 and -3 are expressed constitutively, while their activities are regulated by phosphorylation, S-nitrosylation, protein interaction and cofactor/substrate availability. Conversely, NOS-2 expression is regulated inducibly [13]. NO covalently binds cysteines (S-nitrosylation), heme groups (metal nitrosylation) or tyrosines (nitration) of proteins to regulate their structures and functions. NO binding to the heme group of soluble guanylyl cyclase (sGC) activates its catalytic activity that converts GTP to cGMP. This activates cGMP-dependent protein kinase (PKG), which lowers cellular potassium and calcium ions to hyperpolarize the membrane potential while activating RhoA kinase to suppress contractility [13]. Furthermore

NO S-nitrosylates over 3000 different proteins [14] to regulate their functions. S-nitrosylation protects proteins from ROS-mediated oxidation [sulfonic acid (RSO_3H)] [15] and facilitates disulfide bond formation [16]. (Very high levels of ROS and NO, however, could form peroxynitrite ($ONOO^-$) that damages tissues [17]). In addition, S-nitrosylation triggers structural change of proteins [18], enabling their further post-translational modifications such as phosphorylation [19,20], acetylation and ubiquitination [14].

It has been long known that NO regulates morphogenesis of diverse organisms from invertebrates to rodents [21,22]. NO controls polarity formation by negatively regulating cell division and movement through suppression of RhoA via S-nitrosylation [23]. In addition, NO regulates cell-cell junctions, where NOS is associated with tight junction proteins (e.g., occludin) [24]. NOS-1 and -3 are part of complexes involved in mechano-transduction of neurons and vasculatures, respectively [25,26], which is closely linked to morphogenesis [27]. In particular, NOS-1 interacts with the polarity proteins Scribble and DLG4 [28,29], which co-localize with and stabilize adherens junctions [30,31]. NO plays specific roles in the breast. Increased amount of NO is produced by the postpartum mammary gland [32], which promotes blood flow and nutrient uptake of lactating mammary glands [33] while being also secreted into the breast milk as an essential component for the neonatal growth [34]. In fact, NOS-1 level is elevated in mammary glands during pregnancy [35]. Further, we found that normal virgin mammary glands produce increased level of NO and that such an increase in NO level is required for proper mammary morphogenesis during puberty and establishment of ECM components (manuscript submitted). Conversely, we found that the inhibition of NO production impairs mammary gland development and induces ECM stiffening and premalignant lesions (manuscript submitted). NO production is reduced in many chronic disorders (obesity, diabetes and hypertension) due to oxidative depletion of the NOS cofactor, tetrahydrobiopterin (BH_4) [36], leading to ECM fibrosis and stiffening [37] that increase cancer risks of the patients [38]. A similar mechanism might function (for reducing NO production) to initiate breast tumor.

Despite such a critical role of NO in normal tissue development, there has been a wide-spread controversy over NO's biphasic [pro- vs. anti-tumor] roles in cancer biology [39-42]. For example, NOS-2 level is elevated in advanced cancers [43], whereas its gene knockout exacerbates tumor incidence in tumor-prone animals [44]. Such a contradiction has recently been attributed to a pro- or anti-tumor action of NO depending on the dose and context [45]. At a lower dose (<200 nM), NO is pro-tumoral, activating ERK, AKT, MMP9 and HIF1α, whereas at a higher dose (>200 nM) NO is anti-tumoral, activating the p53 pathway [46]. NO level can be controlled by the substrate and cofactor availability [36], but not by the NOS level, against most NO studies. Using cell lines of breast cancer progression series, we have recently found that NO level declines during the normal to premalignant progression and remains low in the low grade tumor cells. However, NO level again increases in the metastatic breast tumor cells (unpublished data). Such a biphasic expression pattern of NO during breast cancer progression suggests its dual roles as a tumor suppressor and promotor depending on the context, in a manner similar to TGFβ [47]. We hope that our study will at least clarify the role of NO in breast tumor initiation.

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