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Can Neural Signals Override Cellular Decisions in the Presence of DNA Damage?

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Abstract

Cells within an organism are in constant crosstalk with their surrounding environment. Short and long-range signals influence cellular behavior associated with division, differentiation, and death. This crosstalk among cells underlies tissue renewal to guarantee faithful replacement of old or damaged cells over many years. Renewing tissues also offer recurrent opportunities for DNA damage and cellular transformation that tend to occur with aging. Most cells with extensive DNA damage have limited options such as halting cell cycle to repair DNA, undergo senescence, or programmed cell death. However, in some cases cells carrying toxic forms of DNA damage survive and proliferate. The underlying factors driving survival and proliferation of cells with DNA damage remain unknown. Here we discuss potential roles the nervous system may play in influencing the fate of cells with DNA damage. We present a brief survey highlighting the implications the nervous system has in regeneration, regulation of stem cells, modulation of the immune system, and its contribution to cancer progression. Finally, we propose the use of planarian flatworms as a convenient model organism to molecularly dissect the influence of neural signals over cellular fate regulation in the presence of DNA damage.

Keywords

planarians; DNA damage response; nervous system; neural regulation; stem cells; animal models

1. Introduction

One of the most detrimental types of DNA damage are double stranded breaks (DSBs) [1–3]. The presence of DSBs could be lethal; thus, a timely DNA damage response (DDR) is activated to determine the fate of the cell. The cells carrying DSBs have limited options to choose between temporarily halting the cell cycle and repairing DSBs, transitioning into senescence a state in which cells are metabolically active but no longer participate in

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Conflict of Interest Statement

The authors declare there is no conflict of interest.

proliferation, or undergo programmed cell death [4–6]. Under some circumstances, cells with DSBs evade the canonical fates and proliferate, which may contribute to cancer development (Figure 1). While the molecular players mediating the canonical fates of cells with DNA damage have been extensively studied, the underlying mechanisms mediating survival and growth of cells harboring toxic DSBs remain largely unknown.

The survival and proliferation of cells with DSBs is rare and challenging to anticipate. Nonetheless, tissues with high cellular turnover along with aging are predisposing conditions to dividing cells with DSBs and cancer [[7]-[8]]. Indeed, DNA damage is among the earliest manifestations of cellular transformation and is a pervasive feature of human cancers [[9]-[10]]. The renewal of tissues relies on a delicate coordination of cellular events including division, migration, differentiation, and death that are mediated by short-and-long range signals within the body [[11]-[12]]. The continuous crosstalk among cells along with the environmental cues from other tissues may have overriding capacities to alter the fate of cells [[11]-[13]]. The nervous system, for example, facilitates the effective communication and coordination of cellular behavior that is needed to maintain body homeostasis [[14]-[15]]. We emphasize a variety of regulatory roles the nervous system exerts over cells and organs in the adult body in health and disease.

Recently developed experimental model systems facilitate *in situ* analysis of tissue renewal in the presence of cells carrying DSBs [[16]-[17]]. These studies are based on planarian flatworms subjected to genetic manipulations leading to the survival and proliferation of cells with DSBs under high demands for cellular turnover. Uniquely, the planarian system facilitates studies of cellular turnover across the whole adult animal, which includes the influence of intercellular communications and their possible role in altering the fate of cells with DSBs. Recent evidence obtained from experimentation with different animals supports the idea that short-and-long signals from the nervous system regulate the behavior of stem cells, the immune system, and even the fate of regenerating tissues [[11],[18]-[19]]. Based on these findings, we propose the use of planarians as model system to molecularly dissect the contribution of neural signals in the proliferation of cells with DSBs.

2. The cellular response to the presence of DNA double stranded breaks

DNA double stranded breaks (DSBs) are lesions that can have grave consequences to genomic integrity if not repaired. The pathways involved in DSBs repair have been reviewed elsewhere [20]. Here we briefly highlight some of these pathways involving alternative end joining, single strand annealing, homologous recombination and nonhomologous end joining [[21, 22]].

A remarkable difference between nonhomologous end joining and alternative end joining is that nonhomologous end joining is Ku dependent, alternative end joining relies on PARP-1 activation for recruiting alternative end joining factors [[23]-[24] [25][26]]. Alternative end joining is constantly competing with nonhomologous recombination through Parp-1 and Ku, but studies have found that irradiated cells prefer Ku [23, 25]. Alternative end joining contributes to DNA repair when nonhomologous end joining shows limited functionality [[23, 27]]. Homologous recombination is usually triggered during the S and G2/M phases

and requires a homologous DNA sequence as a template, which results in more accurate repair than its counterpart [2–3, 28–29]. Nonhomologous end joining occurs during the G0/G1 and G2/M phases [30]. Unlike homologous recombination, nonhomologous end joining is known to contribute to insertions and deletions at the sites in which the damage has occurred [28]. Nonhomologous end joining is rapid, does not require a template, and is error prone [31–32]. Recent studies have demonstrated these repair pathways appear highly conserved in the planarian flatworms, which is an emerging model organism amenable to studies of stem cells, tissue regeneration, cancer, and the DNA damage response [16–17, 18, 20–21].

3. Neural regulation influences the cellular responses in health and disease

The nervous system exerts regulatory roles over organs and tissues. This notion has been expanded to include neural modulation over the immune system, tissue regeneration, and diseases such as cancer [33–34]. Furthermore, recent evidence demonstrates resident microorganisms can establish “direct conversations” with the nervous system of the host, and these exchanges are critical for behavioral conditions such as autism [13]. Thus, the nervous system is a natural regulator and coordinator of cellular functions to maintain body homeostasis, prevent infections, while facilitating crosstalk across tissues. In some circumstances, the nervous system could impose overriding signals favoring proliferation of abnormal cells [17–16]. Below, we briefly mention few examples associating neural regulation in health and disease with the intention of providing grounds for the integration of the nervous system as a possible modulator of the DNA damage response [35]. For example, melatonin a molecule secreted by the pineal gland functions as a reactive oxygen species scavenger and reduces free radicals by activating antioxidant enzymes, inhibiting prooxidative enzymes through epigenetics. [36–38]. We also suggest potential scenarios whereby neural inputs could lead to the survival and proliferation of cells with DSBs (Figure 1).

3.1 Neural signaling regulates cell behavior

Neural signaling can regulate the behavior of cells through a long-range communication in which signals from the brain influence cellular division, migration, and differentiation in distant parts of the body. There are diverse mechanisms for such neural regulation and one of the best known is the role the sympathetic nervous system plays over hematopoietic stem cells [39–40]. Sympathetic nerves are closely associated with hematopoietic stem and progenitor cells through the neuro-reticular complex that serves as a hub for exchange of information through gap junctions [40–41]. Neurotrophic and neuropeptides factors are released by the sympathetic nerve fibers to regulate hematopoietic stem cell proliferation both positively and negatively [34,42–43]. For example, the neuropeptide substance P mediates proliferation of hematopoietic progenitors, while neurokinin A binding to NK-2 receptors has inhibitory effects on proliferation of granulocytic-monocytic progenitors [34]. Neural regulation of hematopoietic stem cells is also associated with circadian regulation of hypocretin (orexin), which is a neuropeptide hormone produced in the hypothalamus during

sleep [11]. Fragmented sleep leads to insufficient production of hypocretin and increase in myelopoiesis by enhanced CSF1 production [11].

In addition, non-myelinating Schwann cells are capable of maintaining hematopoietic stem cells in quiescence by activating TGF-beta and SMAD signaling [44]. Treatment with pharmacological compounds targeting neural receptors provides an opportunity to modulate stem cell function. For example, treatment with agonists and antagonists (e.g., BRL37344 and SR59230A, respectively) compounds of adrenoreceptors (B3) can increase or decrease transcriptional activity for the chemokine CXCL12 -a critical factor influencing migration of hematopoietic progenitors, stem cells, leukocytes, and endothelial cells [40,45]. The sympathetic nervous system could also regulate bone turnover through leptin, which serves as an anti-osteogenic factor by activation of β2 adrenergic receptors[46–47].

Recent results demonstrate the nervous system also processes inputs from resident bacteria, and these interactions influence behavioral conditions such as autism. Autism spectrum disorder is a neurodevelopmental disorder that is influenced by genetic and environmental factors [13]. Recent evidence suggests microbes residing in the digestive system, specifically *L. reuteri*, could change antisocial behaviors in autism spectrum disorder mice models [13]. This intriguing finding establishes a bidirectional gut-microbiota-brain axis capable of affecting organismal function by way of the vagus nerve and acting on the release of oxytocin [13]. Altogether, these few examples illustrate a diverse repertoire of mechanisms by which neural inputs can influence fate decisions in specific stem cell populations and organismal behavior. Nonetheless, the hierarchical regulation of neural signals over cell fate is unknown.

Perhaps one of the most remarkable examples of neural regulation in cell fate comes from studies of tissue regeneration. Urodele amphibians (e.g., newts and salamanders) are well known for their capacity to regenerate appendages such as limbs. Nerve dependence in regeneration has been extensively studied but the molecular basis underlying this process remain largely unknown [18, 48–51]. It is well known that neural input stimulates limb regeneration (e.g., neuregulin, nAG, BMP2, FGFs), and additional evidence implicate signals from the immune system and cells surrounding the injury may also contribute to tissue repair [18,50–53]. Thus, neural signals are likely integrated with other cues to coordinate limb regeneration. A compelling demonstration about neural modulation of tissue fate was obtained in experiments analyzing regeneration in planarians [54]. The authors of the study show that the nervous system together with three gap junction proteins determine the fate of regenerated tissue in planarians. Furthermore, the findings demonstrate neural cues override the pre-existing axial polarity in the animal, which is shown by the regeneration of ectopic heads including functional brains every time planarians are amputated [54]. These findings suggest long-range neural cues provide overriding instructions to stem cells capable of altering the axial polarity of the whole organism. This long-range gap junctional signaling also facilitate overriding cues leading to tumorigenesis in *Xenopus*, arguing for an evolutionarily conserved signaling mechanism [55].

3.2 Neural signaling regulates the immune system and cancer:

The nervous and immune systems crosstalk includes neural, hormonal, and paracrine signaling. Studies have found that cholinergic fibers are in close contact with immune cells within the gut-associated lymphoid tissue [56]. These cholinergic fibers suppress production of TNF and that these immune cells contain the α7 muscarinic receptor [57–58]. Signaling of the nervous system to the immune system is also done through neurotransmitters like the catecholamines [59]. Both innate and adaptive immune cells contain adrenergic receptors that can enhance or limit the production of inflammatory cytokines [60–62]. Thus, the immune and nervous systems are in a constant crosstalk to facilitate systemic responses and effective ways to combat infections through neuroimmunomodulation (Figure 2A).

Growing evidence indicate that a variety of cancer cells display nerve dependence [18,33,63–64]. Denervation experiments suggest some cancers rely in neural inputs to engage tumorigenesis and metastasize. Given that DNA damage is a pervasive feature of most cancers, we posit that neural regulation may influence the response to DNA damage and/or the fate of transformed cells. Some cancer cells express neurotrophic growth factors and receptors, which influence their survival and growth. Cancer cells are capable of secreting axon guidance molecules such as netrins, ephrin, and slit-robo [65–66]. Netrins facilitate the activation of a variety of pathways such as YAP signaling pathway, PI3K/AKT, ERK/MAPK that enhance cell division. In gastric cancer nerves that reach the site in which tumors form begin to stimulate the enteric nervous system. Stimulation of the enteric nervous system begin the release of a variety of neurotransmitters that aid in various functions [67].

Neurotransmitters are essential components for neural communication, and they can contribute to tumorigenesis. Catecholamines, for example, have been shown to promote tumor growth by activating EGFR signaling, invasion by activating β2 adrenergic receptor-snail signaling, and angiogenesis through secretion of Ephrin [68–69]. Cancer cells are capable of synthesizing and releasing acetylcholine to promote cell proliferation [67,70–71]. Acetylcholine promotes cell proliferation by activating the EGFR-AKT signaling pathway [72]. Acetylcholine is also capable of inducing $Lgr5^+$ stem cells in the gastric tract to proliferate [67,71]. These stem cells contain an abundance of muscarinic acetylcholine receptor 3 making them sensitive to acetylcholine secretion [67,71]. The inhibitory neurotransmitter GABA is able to promote proliferation of carcinoma cells through a paracrine and autocrine fashion [73]. Cholinergic and GABAergic neurons have shown to promote cell growth in cancer cells, and Serotonergic neurons remain to be further studied [71–73]. The mechanistic details about these neural influences over cancer behavior is still under investigation. This brings the possibility of neural inputs as critical regulators of cell behavior with the potential to override cell fate in the presence of DNA damage (Figure 2B).

3.3 Neural signaling as potential regulator of cell fate in the presence of DNA damage

Under stressful circumstances the nervous system releases catecholamines such as dopamine, epinephrine (adrenaline), and norepinephrine (noradrenaline). It is believed that continuous stress leads to accumulation of DNA damage, degenerative conditions and cancer. Recent evidence suggest the increase in DNA damage under chronic stress

is mediated by beta-adrenergic catecholamines that suppress DNA damage repair and p53-induced apoptosis [74–75]. A pathway that may play a role in this function is the β-arrestin-induced activation of AKT signaling [75–76]. This pathway stimulates E3 ubiquitin ligase murine double minute-2 to degrade the p53 protein which in turn inhibits the normal function of p53 chromosomal damage [75]. Studies in which the β-adrenergic receptor is blocked by pharmacological compounds propranolol can effectively up regulate p53 and induce apoptosis [77]. This raises the intriguing possibility about the nervous system serving as mediator in the survival of cells with DNA instability.

The notion that neural signals contribute to the survival of cells with DNA damage, in particular those with DSBs was reinforced by recent studies using planarian flatworms [16–17]. Genetic disturbance with RNA-interference of Rad51 (essential for DSB repair through homologous recombination) and Ubc9 (critical for SUMOylation signaling) lead to systemic increases in DSB across the planarian body [78–79]. Rad51 involvement in DNA repair binds onto the single strands and is involved in the search for the homologous strand thus initiating HR. Intriguingly, there is a differential response along the anteroposterior axis, whereby cells with DSBs survive in the anterior region while there is massive cell death in the posterior part of the planarian (Figure 3A). The survival and proliferation of cells with DSBs in the anterior region of animals subjected to RNAi of *Rad51* and *Ubc9* provide unique opportunities to dissect the underlying mechanisms. Gene expression analysis suggest that *Rb* more than *p53* play a central role in the survival of cells carrying DSBs [78]. Another line of evidence suggests that neural signals from the planarian brain promote the proliferation of cells with DSBs. Disturbance with RNAi of the Wnt signaling pathway (i.e., *ß-catenin* and *APC*) leads to fully anteriorized or posteriorized planarians (i.e., bipolar heads or bipolar tails) [80–81]. Experiments with fully anteriorized and posteriorized planarians are useful to address topographical contribution and dysfunctional Rad51. Double-RNAi with Rad51 in bipolar heads display more cells dividing than in the bipolar tails (Figure 3B) [16]. However, forcing ectopic brain tissue through genetic means into bipolar tail organisms led to a change in cellular fate characterized by cell division with DSBs but only in the surrounding brain tissue (Figure 3B). The results imply neural inputs may alter the fate of cells that were initialed signaled to die into entering cell cycle carrying DSBs in the vicinity of the brain. The results also suggest that a particular type of stem cell is likely involved in these events, but additional experimentation is needed to characterize the cell type and the neural source promoting proliferation of cells with DSBs [16]. The molecular mechanism behind the possible neural regulation of cell with DBS are still unknown, but the results in planarians are consistent with regional differences in the proliferation of normal and neoplastic cells in the anterior region of mice (i.e., head and thoracic cavity), suggesting a possible evolutionary conservation [82–83]. We propose regional differences in the proliferation of cells is facilitated by neural signals originated in the brain and that these neural cues have the capacity to override decisions to proliferate in a particular subset of cells. Additional studies in the planarian model could assist in dissecting the molecular mechanism underlying this process.

4. Planarian is a convenient model organism to study neural influence in DNA damage and repair

The planarian flatworm is an emerging model organism well known for their regenerative capacity and accessible pool of somatic stem cells called neoblasts. These organisms are easy to culture in the laboratory and have a complex body plan including diverse tissues and systems (e.g., muscle, digestive, nervous, etc,) [84–85]. The planarian nervous system includes extensive conservation of neurotransmitters found in humans [84–86]. The neoblast is the only cell with capacity to divide in planarians and is responsible for maintaining all differentiated tissues and the repair during injury. DNA repair mechanisms in planarians are evolutionarily conserved to the point that antibodies against human proteins (e.g., RAD51) can be used in planarians. As mentioned above, there is extreme plasticity of the planarian body plan that can be used to understand regional influence over cell fate. Planarians also display evolutionary conservation of tumor suppressor genes and develop cancer-like phenotypes, which facilitate *in situ* studies about the role of DNA damage and repair at early stages of cellular transformation. Thus, further studies in planarians would be able to provide insights about the molecular crosstalk among tissues and the influence nervous tissue may have over cellular fate decisions in the presence of DNA damage.

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Abbreviations:

DSB	Double Stranded Breaks
DDR	DNA Damage Response
HR	Homologous Recombination
CSF1	Colony Stimulating Factor 1
TGF-β	Transforming Growth Factor Beta
BMP2	Bone Morphogenetic Protein 2
FGF	Fibroblast Growth Factor
NK-2	Neurokinin 2
TNF	Tumor Necrosis Factor

EGFR	Epidermal Growth Factor Receptor
Rb	Retinoblastoma Protein

References

1. Blackford AN, Jackson SP. ATM, ATR, and DNA-PK: The Trinity at the Heart of the DNA Damage Response. Mol Cell. 2017;66(6):801–17. doi: 10.1016/j.molcel.2017.05.015. [PubMed: 28622525]
2. Lodovichi S, Bellè F, Cervelli T, Lorenzoni A, Maresca L, Cozzani C, et al. Effect of BRCA1 missense variants on gene reversion in DNA double-strand break repair mutants and cell cycle-arrested cells of Saccharomyces cerevisiae. Mutagenesis. 2020;35(2):189–95. doi: 10.1093/mutage/gez043. [PubMed: 31769492]
3. Wright WD, Shah SS, Heyer WD. Homologous recombination and the repair of DNA double-strand breaks. J Biol Chem. 2018;293(27):10524–35. Epub 2018/03/29. doi: 10.1074/jbc.TM118.000372. [PubMed: 29599286]
4. Giglia-Mari G, Zotter A, Vermeulen W. DNA damage response. Cold Spring Harb Perspect Biol. 2011;3(1):a000745. Epub 2011/01/01. doi: 10.1101/cshperspect.a000745. [PubMed: 20980439]
5. d'Adda di Fagagna F. Living on a break: cellular senescence as a DNA-damage response. Nat Rev Cancer. 2008;8(7):512–22. doi: 10.1038/nrc2440. [PubMed: 18574463]
6. Tanner C. Curriculum revolution: the practice mandate. NLN Publ. 1988;(15–2224):201–16.
7. da Silva PFL, Schumacher B. DNA damage responses in ageing. Open Biol. 2019;9(11):190168. Epub 2019/11/20. doi: 10.1098/rsob.190168. [PubMed: 31744423]
8. Liu S, Edgerton SM, Moore DH, Thor AD. Measures of cell turnover (proliferation and apoptosis) and their association with survival in breast cancer. Clin Cancer Res. 2001;7(6):1716–23. [PubMed: 11410511]
9. Jackson SP, Bartek J. The DNA-damage response in human biology and disease. Nature. 2009;461(7267):1071–8. doi: 10.1038/nature08467. [PubMed: 19847258]
10. Chen L, Liu P, Evans TC, Ettwiller LM. DNA damage is a pervasive cause of sequencing errors, directly confounding variant identification. Science. 2017;355(6326):752–6. doi: 10.1126/science.aai8690. [PubMed: 28209900]
11. McAlpine CS, Kiss MG, Rattik S, He S, Vassalli A, Valet C, et al. Sleep modulates haematopoiesis and protects against atherosclerosis. Nature. 2019;566(7744):383–7. Epub 2019/02/13. doi: 10.1038/s41586-019-0948-2. [PubMed: 30760925]
12. Zahalka AH, Arnal-Estapé A, Maryanovich M, Nakahara F, Cruz CD, Finley LWS, et al. Adrenergic nerves activate an angio-metabolic switch in prostate cancer. Science. 2017;358(6361):321–6. doi: 10.1126/science.aah5072. [PubMed: 29051371]
13. Sgritta M, Dooling SW, Buffington SA, Momin EN, Francis MB, Britton RA, et al. Mechanisms Underlying Microbial-Mediated Changes in Social Behavior in Mouse Models of Autism Spectrum Disorder. Neuron. 2019;101(2):246–59.e6. Epub 2018/12/03. doi: 10.1016/j.neuron.2018.11.018. [PubMed: 30522820]
14. Roh E, Song DK, Kim MS. Emerging role of the brain in the homeostatic regulation of energy and glucose metabolism. Exp Mol Med. 2016;48:e216. Epub 2016/03/11. doi: 10.1038/emm.2016.4. [PubMed: 26964832]
15. Goldstein DS, Kopin IJ. Homeostatic systems, biocybernetics, and autonomic neuroscience. Auton Neurosci. 2017;208:15–28. Epub 2017/09/05. doi: 10.1016/j.autneu.2017.09.001. [PubMed: 28918243]
16. Peiris TH, Ramirez D, Barghouth PG, Ofoha U, Davidian D, Weckerle F, et al. Regional signals in the planarian body guide stem cell fate in the presence of genomic instability. Development. 2016;143(10):1697–709. Epub 2016/03/24. doi: 10.1242/dev.131318. [PubMed: 27013241]
17. Thiruvalluvan M, Barghouth PG, Tsur A, Broday L, Oviedo NJ. SUMOylation controls stem cell proliferation and regional cell death through Hedgehog signaling in planarians. Cell Mol Life Sci. 2018;75(7):1285–301. Epub 2017/11/02. doi: 10.1007/s00018-017-2697-4. [PubMed: 29098326]
18. Boilly B, Faulkner S, Jobling P, Hondermarck H. Nerve Dependence: From Regeneration to Cancer. Cancer Cell. 2017;31(3):342–54. doi: 10.1016/j.ccell.2017.02.005. [PubMed: 28292437]

19. Currie KW, Molinaro AM, Pearson BJ. Neuronal sources of. Elife. 2016;5. Epub 2016/11/19. doi: 10.7554/eLife.19735.
20. Barghouth PG, Thiruvalluvan M, LeGro M, Oviedo NJ. DNA damage and tissue repair: What we can learn from planaria. Semin Cell Dev Biol. 2019;87:145–59. Epub 2018/05/03. doi: 10.1016/j.semcdb.2018.04.013. [PubMed: 29727725]
21. Goodarzi AA, Jeggo PA. The repair and signaling responses to DNA double-strand breaks. Adv Genet. 2013;82:1–45. doi: 10.1016/B978-0-12-407676-1.00001-9. [PubMed: 23721719]
22. Scott SP, Pandita TK. The cellular control of DNA double-strand breaks. J Cell Biochem. 2006;99(6):1463–75. doi: 10.1002/jcb.21067. [PubMed: 16927314]
23. Ceccaldi R, Rondinelli B, D'Andrea AD. Repair Pathway Choices and Consequences at the Double-Strand Break. Trends Cell Biol. 2016;26(1):52–64. Epub 2015/10/01. doi: 10.1016/j.tcb.2015.07.009. [PubMed: 26437586]
24. Sallmyr A, Tomkinson AE. Repair of DNA double-strand breaks by mammalian alternative end-joining pathways. J Biol Chem. 2018;293(27):10536–46. Epub 2018/03/12. doi: 10.1074/jbc.TM117.000375. [PubMed: 29530982]
25. Deriano L, Roth DB. Modernizing the nonhomologous end-joining repertoire: alternative and classical NHEJ share the stage. Annu Rev Genet. 2013;47:433–55. Epub 2013/09/11. doi: 10.1146/annurev-genet-110711-155540. [PubMed: 24050180]
26. Corneo B, Wendland RL, Deriano L, Cui X, Klein IA, Wong SY, et al. Rag mutations reveal robust alternative end joining. Nature. 2007;449(7161):483–6. doi: 10.1038/nature06168. [PubMed: 17898768]
27. Wang H, Rosidi B, Perrault R, Wang M, Zhang L, Windhofer F, et al. DNA ligase III as a candidate component of backup pathways of nonhomologous end joining. Cancer Res. 2005;65(10):4020–30. doi: 10.1158/0008-5472.CAN-04-3055. [PubMed: 15899791]
28. Ranjha L, Howard SM, Cejka P. Main steps in DNA double-strand break repair: an introduction to homologous recombination and related processes. Chromosoma. 2018;127(2):187–214. Epub 2018/01/11. doi: 10.1007/s00412-017-0658-1. [PubMed: 29327130]
29. Mazur AK, Nguyen TS, Gladyshev E. Direct Homologous dsDNA-dsDNA Pairing: How, Where, and Why? J Mol Biol. 2020;432(3):737–44. Epub 2019/11/11. doi: 10.1016/j.jmb.2019.11.005. [PubMed: 31726060]
30. Roth DB, Wilson JH. Relative rates of homologous and nonhomologous recombination in transfected DNA. Proc Natl Acad Sci U S A. 1985;82(10):3355–9. doi: 10.1073/pnas.82.10.3355. [PubMed: 2987922]
31. Nogueira A, Fernandes M, Catarino R, Medeiros R. Functions in Homologous Recombination and Its Importance on Genomic Integrity Maintenance and Cancer Therapy. Cancers (Basel). 2019;11(11). Epub 2019/10/23. doi: 10.3390/cancers11111622.
32. Biau J, Chautard E, Verrelle P, Dutreix M. Altering DNA Repair to Improve Radiation Therapy: Specific and Multiple Pathway Targeting. Front Oncol. 2019;9:1009. Epub 2019/10/10. doi: 10.3389/fonc.2019.01009. [PubMed: 31649878]
33. Wang K, Zhao XH, Liu J, Zhang R, Li JP. Nervous system and gastric cancer. Biochim Biophys Acta Rev Cancer. 2020;1873(1):188313. Epub 2019/10/21. doi: 10.1016/j.bbcan.2019.188313. [PubMed: 31647986]
34. Greco SJ, Corcoran KE, Cho KJ, Rameshwar P. Tachykinins in the emerging immune system: relevance to bone marrow homeostasis and maintenance of hematopoietic stem cells. Front Biosci. 2004;9:1782–93. Epub 2004/05/01. doi: 10.2741/1373. [PubMed: 14977586]
35. Majidinia M, Sadeghpour A, Mehrzadi S, Reiter RJ, Khatami N, Yousefi B. Melatonin: A pleiotropic molecule that modulates DNA damage response and repair pathways. J Pineal Res. 2017;63(1). Epub 2017/05/18. doi: 10.1111/jpi.12416.
36. Reiter RJ, Mayo JC, Tan DX, Sainz RM, Alatorre-Jimenez M, Qin L. Melatonin as an antioxidant: under promises but over delivers. J Pineal Res. 2016;61(3):253–78. Epub 2016/09/01. doi: 10.1111/jpi.12360. [PubMed: 27500468]
37. Stehle JH, Saade A, Rawashdeh O, Ackermann K, Jilg A, Sebestény T, et al. A survey of molecular details in the human pineal gland in the light of phylogeny, structure, function

and chronobiological diseases. J Pineal Res. 2011;51(1):17–43. Epub 2011/04/26. doi: 10.1111/j.1600-079X.2011.00856.x. [PubMed: 21517957]

38. Acuña-Castroviejo D, Escames G, Venegas C, Díaz-Casado ME, Lima-Cabello E, López LC, et al. Extrapineal melatonin: sources, regulation, and potential functions. Cell Mol Life Sci. 2014;71(16):2997–3025. Epub 2014/02/20. doi: 10.1007/s00018-014-1579-2. [PubMed: 24554058]
39. Wilson A, Laurenti E, Trumpp A. Balancing dormant and self-renewing hematopoietic stem cells. Curr Opin Genet Dev. 2009;19(5):461–8. Epub 2009/10/05. doi: 10.1016/j.gde.2009.08.005. [PubMed: 19811902]
40. Méndez-Ferrer S, Michurina TV, Ferraro F, Mazloom AR, Macarthur BD, Lira SA, et al. Mesenchymal and haematopoietic stem cells form a unique bone marrow niche. Nature. 2010;466(7308):829–34. doi: 10.1038/nature09262. [PubMed: 20703299]
41. Kunisaki Y, Bruns I, Scheiermann C, Ahmed J, Pinho S, Zhang D, et al. Arteriolar niches maintain haematopoietic stem cell quiescence. Nature. 2013;502(7473):637–43. Epub 2013/10/09. doi: 10.1038/nature12612. [PubMed: 24107994]
42. Tabarowski Z, Gibson-Berry K, Felten SY. Noradrenergic and peptidergic innervation of the mouse femur bone marrow. Acta Histochem. 1996;98(4):453–7. doi: 10.1016/S0065-1281(96)80013-4. [PubMed: 8960309]
43. Fras C, Kravetz P, Mody DR, Heggeness MH. Substance P-containing nerves within the human vertebral body. an immunohistochemical study of the basivertebral nerve. Spine J. 2003;3(1):63–7. doi: 10.1016/s1529-9430(02)00455-2. [PubMed: 14589248]
44. Yamazaki S, Ema H, Karlsson G, Yamaguchi T, Miyoshi H, Shioda S, et al. Nonmyelinating Schwann cells maintain hematopoietic stem cell hibernation in the bone marrow niche. Cell. 2011;147(5):1146–58. doi: 10.1016/j.cell.2011.09.053. [PubMed: 22118468]
45. Janssens R, Struyf S, Proost P. The unique structural and functional features of CXCL12. Cell Mol Immunol. 2018;15(4):299–311. Epub 2017/10/30. doi: 10.1038/cmi.2017.107. [PubMed: 29082918]
46. Ducy P, Amling M, Takeda S, Priemel M, Schilling AF, Beil FT, et al. Leptin inhibits bone formation through a hypothalamic relay: a central control of bone mass. Cell. 2000;100(2):197–207. doi: 10.1016/s0092-8674(00)81558-5. [PubMed: 10660043]
47. Takeda S, Elefteriou F, Levasseur R, Liu X, Zhao L, Parker KL, et al. Leptin regulates bone formation via the sympathetic nervous system. Cell. 2002;111(3):305–17. doi: 10.1016/s0092-8674(02)01049-8. [PubMed: 12419242]
48. Vieira WA, Wells KM, McCusker CD. Advancements to the Axolotl Model for Regeneration and Aging. Gerontology. 2020;66(3):212–22. Epub 2019/11/30. doi: 10.1159/000504294. [PubMed: 31779024]
49. Satoh A, Mitogawa K, Makanae A. Nerve roles in blastema induction and pattern formation in limb regeneration. Int J Dev Biol. 2018;62(9–10):605–12. doi: 10.1387/ijdb.180118as. [PubMed: 30378384]
50. Kumar A, Brockes JP. Nerve dependence in tissue, organ, and appendage regeneration. Trends Neurosci. 2012;35(11):691–9. Epub 2012/09/16. doi: 10.1016/j.tins.2012.08.003. [PubMed: 22989534]
51. Satoh A, Mitogawa K, Makanae A. Regeneration inducers in limb regeneration. Dev Growth Differ. 2015;57(6):421–9. Epub 2015/06/23. doi: 10.1111/dgd.12230. [PubMed: 26100345]
52. Kumar A, Godwin JW, Gates PB, Garza-Garcia AA, Brockes JP. Molecular basis for the nerve dependence of limb regeneration in an adult vertebrate. Science. 2007;318(5851):772–7. doi: 10.1126/science.1147710. [PubMed: 17975060]
53. Lehrberg J, Gardiner DM. Regulation of Axolotl (Ambystoma mexicanum) Limb Blastema Cell Proliferation by Nerves and BMP2 in Organotypic Slice Culture. PLoS One. 2015;10(4):e0123186. Epub 2015/04/29. doi: 10.1371/journal.pone.0123186. [PubMed: 25923915]
54. Oviedo NJ, Morokuma J, Walentek P, Kema IP, Gu MB, Ahn JM, et al. Long-range neural and gap junction protein-mediated cues control polarity during planarian regeneration. Dev Biol. 2010;339(1):188–99. Epub 2009/12/21. doi: 10.1016/j.ydbio.2009.12.012. [PubMed: 20026026]

55. Chernet BT, Fields C, Levin M. Long-range gap junctional signaling controls oncogene-mediated tumorigenesis in Xenopus laevis embryos. Front Physiol. 2014;5:519. Epub 2015/01/19. doi: 10.3389/fphys.2014.00519. [PubMed: 25646081]
56. Gautron L, Rutkowski JM, Burton MD, Wei W, Wan Y, Elmquist JK. Neuronal and nonneuronal cholinergic structures in the mouse gastrointestinal tract and spleen. J Comp Neurol. 2013;521(16):3741–67. doi: 10.1002/cne.23376. [PubMed: 23749724]
57. Ernsberger U, Rohrer H. Development of the cholinergic neurotransmitter phenotype in postganglionic sympathetic neurons. Cell Tissue Res. 1999;297(3):339–61. doi: 10.1007/s004410051363. [PubMed: 10460483]
58. Asmus SE, Parsons S, Landis SC. Developmental changes in the transmitter properties of sympathetic neurons that innervate the periosteum. J Neurosci. 2000;20(4):1495–504. [PubMed: 10662839]
59. Nance DM, Sanders VM. Autonomic innervation and regulation of the immune system (1987–2007). Brain Behav Immun. 2007;21(6):736–45. Epub 2007/04/27. doi: 10.1016/j.bbi.2007.03.008. [PubMed: 17467231]
60. Kolmus K, Tavernier J, Gerlo S. β2-Adrenergic receptors in immunity and inflammation: stressing NF-κB. Brain Behav Immun. 2015;45:297–310. Epub 2014/10/22. doi: 10.1016/j.bbi.2014.10.007. [PubMed: 25459102]
61. Swanson MA, Lee WT, Sanders VM. IFN-gamma production by Th1 cells generated from naive CD4+ T cells exposed to norepinephrine. J Immunol. 2001;166(1):232–40. doi: 10.4049/jimmunol.166.1.232. [PubMed: 11123297]
62. Madden KS, Felten SY, Felten DL, Sundaresan PR, Livnat S. Sympathetic neural modulation of the immune system. I. Depression of T cell immunity in vivo and vitro following chemical sympathectomy. Brain Behav Immun. 1989;3(1):72–89. doi: 10.1016/0889-1591(89)90007-x. [PubMed: 2504310]
63. Makwana M, Raivich G. Molecular mechanisms in successful peripheral regeneration. FEBS J. 2005;272(11):2628–38. doi: 10.1111/j.1742-4658.2005.04699.x. [PubMed: 15943798]
64. Mancino M, Ametller E, Gascón P, Almendro V. The neuronal influence on tumor progression. Biochim Biophys Acta. 2011;1816(2):105–18. Epub 2011/05/14. doi: 10.1016/j.bbcan.2011.04.005. [PubMed: 21616127]
65. Rudno-Rudzińska J, Kielan W, Frejlich E, Kotulski K, Hap W, Kurnol K, et al. A review on Eph/ephrin, angiogenesis and lymphangiogenesis in gastric, colorectal and pancreatic cancers. Chin J Cancer Res. 2017;29(4):303–12. doi: 10.21147/j.issn.1000-9604.2017.04.03. [PubMed: 28947862]
66. Wong SS, Kim KM, Ting JC, Yu K, Fu J, Liu S, et al. Genomic landscape and genetic heterogeneity in gastric adenocarcinoma revealed by whole-genome sequencing. Nat Commun. 2014;5:5477. Epub 2014/11/19. doi: 10.1038/ncomms6477. [PubMed: 25407104]
67. Zhao CM, Hayakawa Y, Kodama Y, Muthupalani S, Westphalen CB, Andersen GT, et al. Denervation suppresses gastric tumorigenesis. Sci Transl Med. 2014;6(250):250ra115. doi: 10.1126/scitranslmed.3009569.
68. Spiegel D, Sephton SE. Psychoneuroimmune and endocrine pathways in cancer: effects of stress and support. Semin Clin Neuropsychiatry. 2001;6(4):252–65. doi: 10.1053/scnp.2001.26995. [PubMed: 11607921]
69. Taylor CB, Conrad A, Wilhelm FH, Neri E, DeLorenzo A, Kramer MA, et al. Psychophysiological and cortisol responses to psychological stress in depressed and nondepressed older men and women with elevated cardiovascular disease risk. Psychosom Med. 2006;68(4):538–46. doi: 10.1097/01.psy.0000222372.16274.92. [PubMed: 16868262]
70. Russo P, Del Bufalo A, Milic M, Salinaro G, Fini M, Cesario A. Cholinergic receptors as target for cancer therapy in a systems medicine perspective. Curr Mol Med. 2014;14(9):1126–38. doi: 10.2174/1566524014666141015152601. [PubMed: 25324001]
71. Rabben HL, Zhao CM, Hayakawa Y, Wang TC, Chen D. Vagotomy and Gastric Tumorigenesis. Curr Neuropharmacol. 2016;14(8):967–72. doi: 10.2174/1570159×14666160121114854. [PubMed: 26791481]

72. Yu H, Xia H, Tang Q, Xu H, Wei G, Chen Y, et al. Acetylcholine acts through M3 muscarinic receptor to activate the EGFR signaling and promotes gastric cancer cell proliferation. Sci Rep. 2017;7:40802. Epub 2017/01/19. doi: 10.1038/srep40802. [PubMed: 28102288]
73. Maemura K, Shiraishi N, Sakagami K, Kawakami K, Inoue T, Murano M, et al. Proliferative effects of gamma-aminobutyric acid on the gastric cancer cell line are associated with extracellular signal-regulated kinase 1/2 activation. J Gastroenterol Hepatol. 2009;24(4):688–96. Epub 2008/11/20. doi: 10.1111/j.1440-1746.2008.05687.x. [PubMed: 19032445]
74. Liao X, Che X, Zhao W, Zhang D, Bi T, Wang G. The β-adrenoceptor antagonist, propranolol, induces human gastric cancer cell apoptosis and cell cycle arrest via inhibiting nuclear factor κB signaling. Oncol Rep. 2010;24(6):1669–76. doi: 10.3892/or_00001032. [PubMed: 21042766]
75. Hara MR, Kovacs JJ, Whalen EJ, Rajagopal S, Strachan RT, Grant W, et al. A stress response pathway regulates DNA damage through β2-adrenoreceptors and β-arrestin-1. Nature. 2011;477(7364):349–53. Epub 2011/08/21. doi: 10.1038/nature10368. [PubMed: 21857681]
76. Venditti C, Pagel M. Plenty of room for punctuational change. Trends Ecol Evol. 2014;29(2):71–2. Epub 2013/12/31. doi: 10.1016/j.tree.2013.12.002. [PubMed: 24388287]
77. Wolter JK, Wolter NE, Blanch A, Partridge T, Cheng L, Morgenstern DA, et al. Anti-tumor activity of the beta-adrenergic receptor antagonist propranolol in neuroblastoma. Oncotarget. 2014;5(1):161–72. doi: 10.18632/oncotarget.1083. [PubMed: 24389287]
78. Peiris TH, Ramirez D, Barghouth PG, Ofoha U, Davidian D, Weckerle F, et al. Regional signals in the planarian body guide stem cell fate in the presence of genomic instability. Development. 2016;143(10):1697–709. doi: 10.1242/dev.131318. [PubMed: 27013241]
79. Thiruvalluvan M, Barghouth PG, Tsur A, Broday L, Oviedo NJ. SUMOylation controls stem cell proliferation and regional cell death through Hedgehog signaling in planarians. Cell Mol Life Sci. 2018;75(7):1285–301. doi: 10.1007/s00018-017-2697-4. [PubMed: 29098326]
80. Reddien PW. Constitutive gene expression and the specification of tissue identity in adult planarian biology. Trends Genet. 2011;27(7):277–85. Epub 2011/06/15. doi: 10.1016/j.tig.2011.04.004. [PubMed: 21680047]
81. Petersen CP, Reddien PW. Smed-betacatenin-1 is required for anteroposterior blastema polarity in planarian regeneration. Science. 2008;319(5861):327–30. Epub 2007/12/06. doi: 10.1126/science.1149943. [PubMed: 18063755]
82. Auerbach R, Morrissey LW, Sidky YA. Regional differences in the incidence and growth of mouse tumors following intradermal or subcutaneous inoculation. Cancer Res. 1978;38(6):1739–44. [PubMed: 647684]
83. Auerbach R, Auerbach W. Regional differences in the growth of normal and neoplastic cells. Science. 1982;215(4529):127–34. doi: 10.1126/science.7053564. [PubMed: 7053564]
84. Gentile L, Cebrià F, Bartscherer K. The planarian flatworm: an in vivo model for stem cell biology and nervous system regeneration. Dis Model Mech. 2011;4(1):12–9. Epub 2010/12/06. doi: 10.1242/dmm.006692. [PubMed: 21135057]
85. Reddien PW, Sánchez Alvarado A. Fundamentals of planarian regeneration. Annu Rev Cell Dev Biol. 2004;20:725–57. doi: 10.1146/annurev.cellbio.20.010403.095114. [PubMed: 15473858]
86. Ross KG, Currie KW, Pearson BJ, Zayas RM. Nervous system development and regeneration in freshwater planarians. Wiley Interdiscip Rev Dev Biol. 2017;6(3). Epub 2017/03/22. doi: 10.1002/wdev.266.

5.

Perspective and Significance.

The DNA damage response leads to timely decisions that are generally assumed at the cellular level. Nonetheless, the influence of the continuous tissue crosstalk and appropriate decisions for cell fate, suggest that there is a need for broadening the context in which decisions to DNA damage are studied. As we learn more about the extended role and processing of information by the nervous system, it is plausible to also broaden the perspective of studies in the DNA damage response to include a more holistic approach. This is even more relevant when the DNA damage response is evaluated *in situ* as cells undergo renewal in the presence of input from distant tissues and the physiological demands of the adult body. The integration of additional expertise, fields of research, and model organisms will likely uncover new areas associated with the DNA damage response relevant to basic biology and clinical intervention.

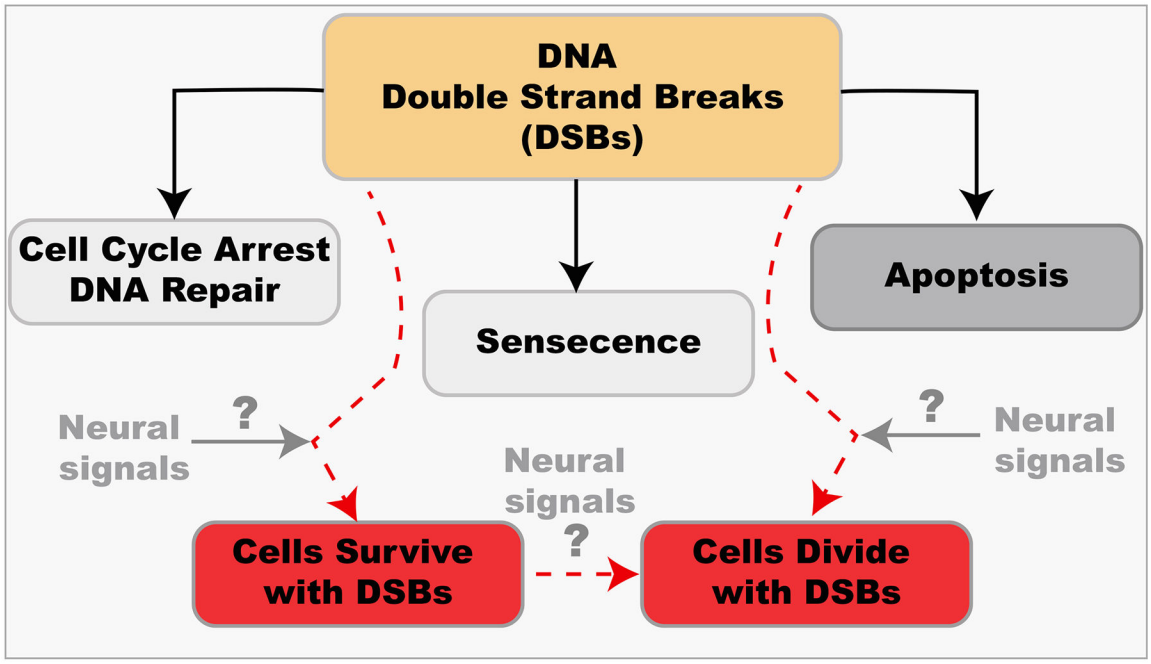

Figure 1: Cellular fate in the presence of DNA Double Stranded Break.

Schematic representation summarizing the different options cells with DNA double stranded breaks (DSBs) may take. The conventional paths (grey boxes) consist of cell cycle arrest with repair of DNA, senescence, and apoptosis. An alternative fourth path (red box) is characterized by cellular survival with DSBs and eventually division with DSBs. We propose neural signals may contribute to the survival and proliferation of cells with DSBs.

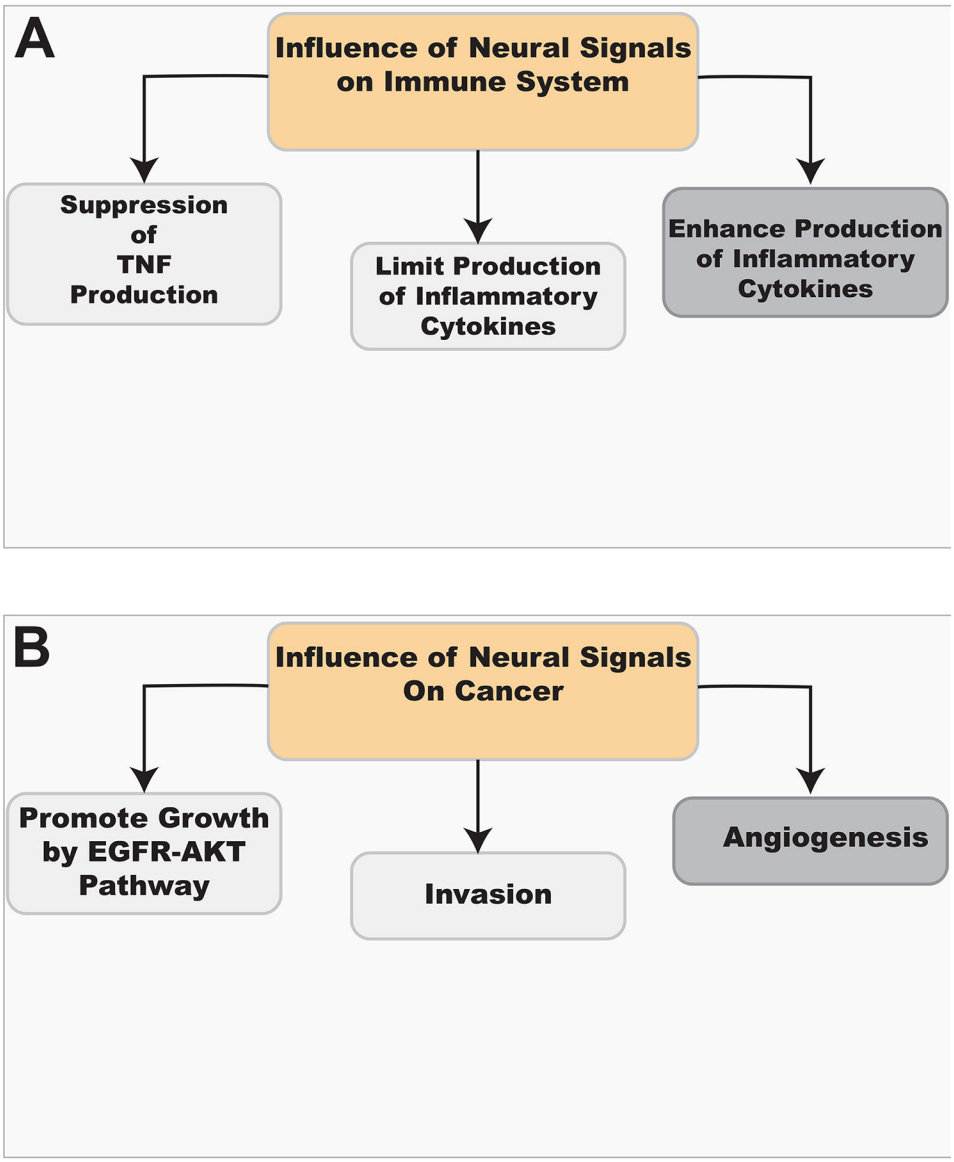

Figure 2: A crosstalk between the body systems and cancer.

Illustration summarizing a hypothetical influence of neural signals over the immune system and cancer cells. (A) Neural signals are capable of suppressing TNF production. Depending on the adrenergic receptors that innate and adaptive immune cells contain neural signals can either limit or enhance the production of inflammatory cytokines. (B) Neural signals are capable of influencing cancer by promoting growth of cells through activation of EGFR-AKT pathway. A variety of neural cell types can influence invasion and angiogenesis.

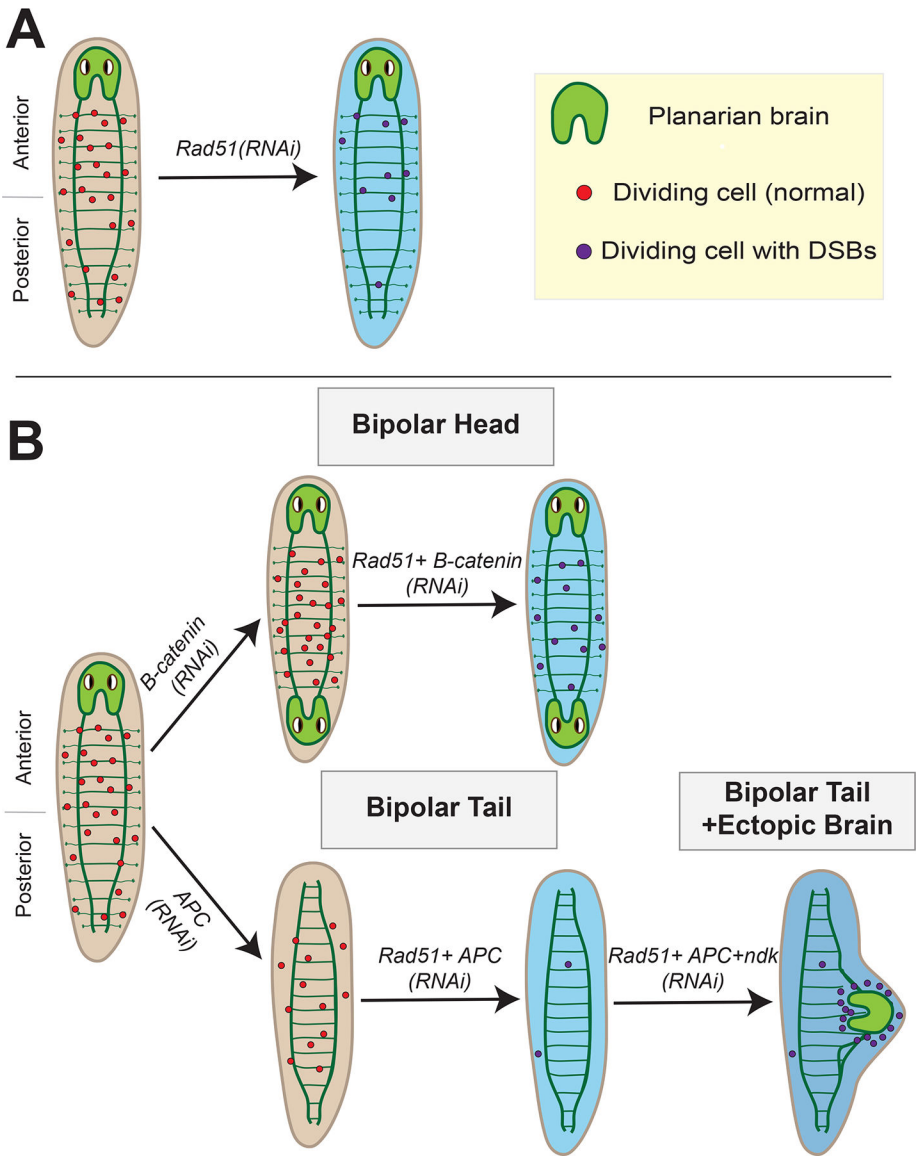

Figure 3: Neural signals promote the survival and proliferation of cells with DSBs.

Illustration summarizing the study in which genetic disruption of *rad51* leads to a decrease in neoblast proliferation. (A) Represents a control animal with normal dividing cells (red dots). Genetic disruption of *Rad51* leads to a systemic increase in cells with DSBs and cell death in the posterior region (not shown). The reduction in Rad51 function is accompanied by decrease of dividing cells that are mostly concentrated in the anterior region of the animal. Importantly, all dividing cells have high levels of DSBs. (B) Genetic disruption of *β-catenin* leads to bipolar headed animals (i.e., one head in each end and no posterior region). Genetic disruption of *apc* leads to bipolar tailed animals (i.e., organisms with only posterior regions and no heads). Disruption of *rad51* was done on both bipolar headed animals and bipolar tailed animals. Comparison of dividing cells showed that bipolar headed animals had more cells dividing with DSBs than in the double tailed animal. Ectopic brain tissue was induced by disrupting the gene nou-darake (ndk) (Cebria et al., 2002) in double tailed

animals subjected to *Rad51(RNAi)*. Interestingly, the presence of brain tissue in a double tailed animal led to an increase in cell division with DSBs and most of the proliferative cells were located surrounding the brain. For more information see Peiris et al., 2016.