

# [Toll-like receptor 9 in breast cancer](https://assignbuster.com/toll-like-receptor-9-in-breast-cancer/)

[](https://assignbuster.com/)[Health & Medicine](https://assignbuster.com/essay-subjects/health-n-medicine/)

## Introduction

Toll-like receptor 9 (TLR9) is a DNA receptor that recognizes microbial and vertebrate DNA ( [1](#B1) – [5](#B5) ). Initially, TLR9 was thought to recognize specifically the CpG sequence in DNA ( [1](#B1) , [6](#B6) ). The sequence-requirement may, however, be relevant only for the synthetic, oligonucleotide TLR9-ligands in the phosphorothioate backbone, and also CpG sequence-independent TLR9 activation by DNA has been reported ( [6](#B6) – [8](#B8) ). Like the other TLRs that recognize nucleic acids (TLR3, TLRs 7–8, and TLR13), TLR9 is located at the endoplasmic reticulum in resting cells ( [9](#B9) , [10](#B10) ). When DNA enters the cell, TLR9 translocates to the endosomal/lysosomal compartment where ligand recognition and binding takes place ( [9](#B9) , [11](#B11) ). DNA recognition by TLR9 initiates a downstream signaling cascade, which includes the adaptor molecule MyD88 ( [12](#B12) , [13](#B13) ). As an effector of the innate immune system, stimulation of TLR9 induces a NF-κB-mediated rapid inflammation, characterized by increased expression of various interleukins and cytokines. A common feature for the nucleotide-sensing TLRs is the induction of both antiviral and antitumoral type I interferons (IFNs) from plasmocytoid dendritic cells (pDCs) ( [14](#B14) ). Eventually, this inflammation also activates the adaptive immune system, which then results in the clearance of the invading pathogens and the infected cells ( [2](#B2) , [15](#B15) ). A similar inflammatory response, mediated via TLRs, also takes place during sterile tissue damage ( [16](#B16) – [19](#B19) ). In addition to DNA, other biological molecules have also been suggested to induce TLR9-mediated responses. Such molecules include the malaria pigment hemozoin and histone proteins ( [17](#B17) , [20](#B20) – [22](#B22) ). TLR9 was recently shown also to recognize RNA–DNA hybrids ( [23](#B23) ).

## TLR9 Expression in Breast Cancer

Toll-like receptor 9 expression has been detected in cells of breast milk (TLR9 mRNA) and also in normal epithelial cells of the mammary gland (TLR9 protein) ( [24](#B24) , [25](#B25) ). TLR9 mRNA and protein are also widely expressed in various human cancer-cell lines as well as in clinical cancer specimens, including breast, prostate, brain, gastric, renal cell carcinoma, and esophageal tumors ( [24](#B24) , [26](#B26) – [33](#B33) ). Specifically in breast cancer, TLR9 protein expression has been detected both in the epithelial cancer cells as well as in the fibroblast-like cells associated with the tumors ( [24](#B24) , [26](#B26) , [29](#B29) , [34](#B34) ). Consistent with the endosomal/lysosomal localization of TLR9 at the subcellular level, in breast cancer cells *in vitro* , TLR9 appeared punctate in intracellular fluorescence staining, located especially in the perinuclear region, where these organelles are located ( [35](#B35) ). Of the five human TLR9 isoforms (A–E), mRNA expression of the TLR9 A and B isoforms has been studied and detected in breast cancer specimens ( [36](#B36) , [37](#B37) ).

## TLR9 as a Prognostic Factor in Breast Cancer

The prognostic significance of TLR9 in cancers appears to be bimodal. In some cancers, such as glioma, prostate cancer, and esophageal adenocarcinoma, high tumor TLR9 expression has been associated with poor survival whereas in others, such as triple-negative breast cancer (TNBC) or renal cell carcinoma, low tumor TLR9 expression upon diagnosis predicts poor prognosis ( [27](#B27) , [30](#B30) , [32](#B32) , [33](#B33) , [38](#B38) , [39](#B39) ). We demonstrated recently that although widely expressed in all clinical subtypes of breast cancer, TLR9 expression has significant, prognostic significance only in TNBC that lack the expression of estrogen (ER), progesterone (PR), and HER2 receptors. More specifically, low tumor TLR9 expression upon diagnosis was associated with a significantly shortened disease-free-specific survival ( [29](#B29) , [32](#B32) ). Furthermore, although we demonstrated that low-TLR9–TNBC cells become highly invasive in hypoxic conditions, it is currently unclear whether this mechanism contributes to the poor survival of the breast cancer patients that have hypoxic, low-TLR9–TNBC tumors. The mechanism for the increased invasion in hypoxia when TLR9 is absent is also not known ( [32](#B32) ). In addition to the actual tumor cells, the TLR9 expression status of tumor-associated fibroblast-like cells has also been shown to be of prognostic value in breast cancer. In this context, high TLR9 expression was associated with better prognosis ( [34](#B34) ). This study did not, however, assess triple-negative status of the cancers, and the exclusion of metastatic and neoadjuvant-treated patients probably counter selected against patients of the TNBC subtype.

## Effects of TLR9 Stimulation on Cellular Invasion

Synthetic TLR9-ligands, the CpG sequence-containing oligonucleotides (CpG–ODNs, such as ODN M362) that mimic bacterial DNA, are strong inducers of inflammation in cells of the immune system ( [40](#B40) , [41](#B41) ). These oligonucleotides mimic bacterial DNA based on their high CpG content and unmethylated cytosines. CpG–ODNs are taken up into cells via DEC-205, a multilectin cell surface receptor, which is expressed in various cell types ( [42](#B42) ). These same compounds induce cellular invasion in macrophages, mesenchymal stem cells, and in cancer cells of various origins *in vitro* ( [24](#B24) , [28](#B28) , [43](#B43) , [44](#B44) ). In breast cancer cells, such synthetic TLR9 ligand-induced invasion has been detected both in ER-positive and ER-negative breast cancer cells ( [24](#B24) , [28](#B28) , [35](#B35) ). This invasive effect is mediated via TLR9, and it is blocked by chloroquine, an inhibitor of endosomal acidification and an inhibitor of TLR9 signaling. Downstream of TLR9, such invasion is mediated via TRAF6, but not MyD88 ( [24](#B24) , [28](#B28) , [35](#B35) ). At the proteolytic level, CpG–ODN-induced invasion is associated with down-regulation of tissue inhibitor of matrix metalloproteinases-3 (TIMP-3) and activation of matrix metalloproteinase-13 (MMP-13) ( [24](#B24) , [28](#B28) , [35](#B35) , [44](#B44) ). Interestingly, although methylation of cytosines in CpGs has been shown to decrease their pro-inflammatory effects, the invasive effects of these molecules are independent of their methylation status ( [35](#B35) , [40](#B40) , [45](#B45) ). CpG–ODNs can form various secondary structures, including homopolymer duplexes and hairpins, containing stem loop structures. The stem loop secondary structure appears important for the invasive effects of the CpG–ODN ( [35](#B35) ). Furthermore, the invasive effects can also be seen with non-CpG sequence-containing ODNs that in inflammatory experiments act as TLR9 antagonists ( [24](#B24) , [46](#B46) ). The synthetic, phosphorothioate-backbone-modified CpG–ODNs do not exist in nature. Thus, for this invasion to have physiological significance, it would have to be caused also by natural DNA in the phosphodiester backbone. In prostate cancer cell lines and in gastrointestinal cancer cell lines, bacterial DNA (purified from *Escherichia coli* or *Helicobacter pylori* , respectively) also has similar, stimulatory effects on invasion ( [28](#B28) , [43](#B43) ). Whether microbe-derived DNA similarly induces invasion in breast cancer cells is not known. We, however, demonstrated recently that self-DNA, which is derived from chemotherapy-treated, dead cancer cells is rapidly taken up into surviving cancer cells, where it serves as an invasion-inducing TLR9 ligand ( [47](#B47) ). This cellular uptake is possibly endocytosis or pinocytosis-mediated, since fluorescently labeled, dead cancer-cell-derived DNA, which was added to cell culture medium, was seen inside the recipient cells rapidly, within 15 min. However, similar to other reported TLR9-mediated effects of cell-derived self-DNA, complex formation of such cell-derived DNAs with the cationic antimicrobial peptide LL-37 enhanced DNA uptake into viable breast cancer cells, and was a requirement for the invasion-inducing effects ( [47](#B47) , [48](#B48) ). This scenario may be physiologically relevant since LL-37 is expressed also in breast cancers ( [49](#B49) , [50](#B50) ). Interestingly, the effects of cell-DNA on invasion are mediated via cathepsins and surprisingly, not via MMPs, which are the mediators for CpG–ODN-induced invasion ( [44](#B44) , [47](#B47) , [51](#B51) , [52](#B52) ). DNA that was derived from intact, proliferating cancer cells did not induce invasion. This suggests that the invasive effect requires a certain DNA-structure, either alone or in complex with LL-37. Such DNA-structures could possibly be formed upon DNA degradation by nucleases. Whether self-DNA-induced and TLR9-mediated cancer cell invasion takes place *in vivo* in breast or any cancer is currently unknown. In principle, however, such DNA-induced and TLR9-mediated cancer cell invasion could represent a novel mechanism of treatment resistance. Since tumor growth is the sum of local proliferation and local invasion, such treatment resistance could theoretically manifest as no change or even increase in tumor size despite treatment. Finally, TLR9 appears to have also ligand-independent invasive activity. Down-regulation of TLR9 in MDA-MB-231 breast cancer cells through siRNA results in decreased *in vitro* invasion in the absence of exogenous DNA. The decreased invasion of the TLR9 siRNA cells was associated with decreased MMP activity and increased expression of TIMP-3 ( [32](#B32) ). Similar effects were also detected by TLR9 siRNA in brain cancer cells *in vitro* ( [53](#B53) ). These TLR9 expression-induced changes in the cellular invasive machinery suggest that TLR9, as a DNA-binding protein, might also have effects on gene transcription. TLR9 expression has indeed been detected in the nuclei of renal cell carcinoma tumor samples ( [30](#B30) ), but whether or not it can directly affect gene expression, requires further experimenting.

## Effects of TLR9 Stimulation on Inflammation

Toll-like receptor 9 agonists have various well documented pro-inflammatory effects in cells of the immune system ( [40](#B40) , [41](#B41) , [48](#B48) , [54](#B54) ). Whether synthetic TLR9 agonists also induce the expression of inflammatory mediators in breast cancer cells, is not known. In cells of the immune system, a key characteristic of the TLR9-induced innate immune response is the promotion of a strong type I T helper cell (Th1) adaptive immune response. This includes both CD8 + T-cell responses and antigen-specific antibody responses ( [55](#B55) ). Since CD8 + T-cells are capable of immunologic tumor cell destruction, CpG–ODNs have been tested both as monotherapy and as an adjuvant for cancer vaccines, against various cancer types in pre-clinical cancer models, including breast cancer ( [55](#B55) ). In mouse models of breast cancer, CpG–ODN treatment resulted in the eradication of orthotopic tumors ( [56](#B56) , [57](#B57) ). CpG–ODN treatment also induced an immunologic memory against tumor challenge, which was associated with an up-regulation of IFN-γ-positive CD4 + and CD8 + T-cells ( [56](#B56) , [57](#B57) ). CpGs, when given as an adjuvant with a peptide vaccine, also prevented the formation of spontaneous tumors in a mouse model of HER2-positive breast cancer ( [58](#B58) ). Although the direct growth inhibitory effects of CpG–ODNs on cancer cells are quite weak *in vitro* , certain modifications in the CpG structure have resulted in increased tumor growth inhibition, also in nude mouse models *in vivo* , suggesting direct tumor effects of these compounds ( [24](#B24) , [59](#B59) – [61](#B61) ). Furthermore, when given in a combination, the immunomodulatory ODN was also shown to potentiate the efficacy of trastuzumab, an anti-HER2-antibody, in a mouse model of breast cancer ( [59](#B59) ). In conclusion, these pre-clinical experiments suggest that TLR9 ligands can directly inhibit the growth of breast cancer cells *in vitro* and *in vivo* , and they can enhance anti-tumor immunity, possibly via inducing a Th1 adaptive immune response. These studies have not, however, addressed the role of TLR9 expression in tumors vs. host in these responses. Despite the successful pre-clinical results, CpG treatment has demonstrated anti-tumor activity only in select patients in clinical trials. There are, however, no reports on their efficacy in breast cancer trials ( [55](#B55) ). Finally, the discrepancies between the *in vitro* -observed, unwanted tumor invasion-promoting effects and the favorable, most likely immune system-mediated anti-tumor effects of the synthetic TLR9-ligands are likely explained by the pharmacokinetics of these compounds. After s. c. and i. v. administration, highest concentrations of TLR9 ligands are detected in plasma, kidneys, and organs of the reticuloendothelial system, and much less so in tumor tissues ( [59](#B59) ).

Self-DNA has been shown to have TLR9-mediated inflammatory effects in other cell types, especially when complexed with LL-37, which is expressed in various tissues ( [16](#B16) , [48](#B48) , [52](#B52) , [62](#B62) ). We demonstrated recently that self-DNA, which is derived from doxorubicin-killed breast cancer cells, induces mRNA expression of various inflammatory mediators in living, TLR9-expressing cells. Furthermore, while assessing treatment responses to doxorubicin in a mouse model of TNBC, we discovered that although the tumor response to treatment was similar in TLR9 siRNA and control siRNA TNBC groups, mice bearing TLR9 siRNA tumors lost significantly less weight than similarly treated mice with control siRNA tumors. Similar weights of the vehicle-treated mice suggested to us that TLR9 expression in the tumors may be an important determinant of chemotherapy-induced inflammation and activation of anti-tumor immunity ( [47](#B47) ). Inflammatory response to chemotherapy is gaining acceptance as an important mediator of treatment responses to standard cancer therapy ( [63](#B63) ). More specifically, we hypothesize that the tumor TLR9-dependent, post-treatment weight loss is actually a surrogate marker for self-DNA-induced and TLR9-mediated inflammation that takes place at the tumor site. Such tumor TLR9-mediated inflammation might then amplify the anti-tumor immune response, eradicate microscopic disease and through this mechanism, translate into cure ( [47](#B47) ). We predict that the lack of such immunogenic effect in tumors that have low-TLR9 expression indeed contributes to the described poor disease-specific survival in triple-negative disease ( [32](#B32) ). This hypothesis requires a detailed analysis of tumor TLR9-dependent immune response to chemotherapy in immune-competent pre-clinical cancer models. However, if true, it would mean that patients with low-TLR9–TNBC could especially benefit from adjuvant cancer immunotherapy. It is also possible that TLR9 expression changes tumor immunophenotype independent of treatment and this aspect also requires further investigation.

## TLR9 Regulation in Breast Cancer

Several cancer-associated viruses have been shown to down-regulate TLR9 expression through their oncoproteins. For example, human papillomavirus (HPV), Epstein–Barr virus, and hepatitis B virus inhibit the expression and impair the function of TLR9 in infected target cells ( [64](#B64) – [66](#B66) ). Patients with chronic hepatitis B virus have decreased levels of TLR9 mRNA in peripheral blood mononuclear cells ( [67](#B67) ). The Merkel cell polyomavirus large T antigen down-regulates TLR9 expression in epithelial cells and in cells derived from Merkel cell carcinomas ( [68](#B68) ). For the HPV16, the mechanism behind TLR9 suppression was recently shown to involve the viral oncoprotein E7-induced formation of transcriptional inhibitory complex that includes NF-κB p50–p65, ERα, and chromatin modifying enzymes. This complex induces epigenetic changes at the TLR9 promoter area ( [69](#B69) ). It is likely that these viral effects on TLR9 expression and function play an important role in viral persistence, through inhibition of host immune responses ( [64](#B64) , [65](#B65) , [67](#B67) , [70](#B70) , [71](#B71) ). Nevertheless, also opposite effects on microbial TLR9 regulation have been suggested ( [72](#B72) , [73](#B73) ). Although breast cancer is not currently considered to have viral etiology, several viruses, including human papilloma viruses, have been detected in normal and cancerous human breast tissues ( [74](#B74) – [77](#B77) ). Whether or not these viral effects have a role in breast cancer development or pathophysiology is currently unknown.

Tumor microenvironment oxygen concentration is also an important regulator of TLRs. Similar with the effects of hypoxia on other TLRs in other cell types, hypoxia also up-regulates TLR9 expression in breast cancer cells *in vitro* and in orthotopic breast tumors *in vivo* ( [32](#B32) , [51](#B51) , [78](#B78) ). These hypoxia effects on TLR9 mRNA and protein expression were mediated via HIF-1α in breast cancer cells *in vitro* ( [32](#B32) ). TNBCs are typically hypoxic ( [79](#B79) ). Therefore, understanding the mechanism on why tumor TLR9 expression levels remain low despite hypoxia in some TNBCs might open novel therapeutic possibilities that might also apply to renal cell carcinoma ( [30](#B30) ). It was also demonstrated recently that TLR9 expression is under the control of the circadian molecular clock ( [80](#B80) ). The significance of this finding for breast and other cancers is currently open.

Although TLR9 is expressed in all clinically relevant subtypes of breast cancer, we and others have discovered that there is an inverse correlation between tumor TLR9 and ER expression: ER-positive breast cancers have significantly lower levels of TLR9 expression, as compared with TNBCs ( [26](#B26) , [29](#B29) , [32](#B32) , [36](#B36) ). The basal TLR9 expression is also significantly lower in human ER-positive breast cancer cells, as compared with human ER-negative breast cancer cell lines *in vitro* . Furthermore, transfection of ERα cDNA into TNBC cells suppresses TLR9 expression of the recipient cells ( [36](#B36) ). Both estradiol and testosterone induced TLR9 expression via their cognate receptors in breast cancer cells *in vitro* . Testosterone also augmented the pro-invasive effects of CpG–ODNs. Finally, bicalutamide, a commonly used hormonal treatment in prostate cancer, increased TLR9 expression in ER-positive breast cancer cells ( [36](#B36) ). This effect of bicalutamide on TLR9 expression might be of therapeutic interest since a proportion of TNBC tumors express the androgen receptor that bicalutamide targets ( [81](#B81) ).

## TLR9 Polymorphism in Breast Cancer

The TLR9 gene is located on human chromosome 3 ( [82](#B82) ). Although TLR9 gene polymorphisms have been studied in other diseases, including infectious and autoimmune diseases and some cancers, very little is known about TLR9 gene polymorphism in breast cancer ( [83](#B83) – [86](#B86) ). A study conducted by Resler and coworkers using over 800 case and control samples, found that the single nucleotide polymorphism (SNP, rs352140) in *TLR9* , which does not alter protein amino acid sequence but might alter protein function or stability, was associated with breast cancer risk (OR 0. 85, 95% CI 0. 74–0. 97) ( [87](#B87) ). The patients in this study were all post-menopausal (65–79 years) and 80% of the cases had hormone receptor-positive breast cancer. These results were in contrast to those of Etokebe et al., who found no association in the same TLR9 SNP with breast cancer risk in a small Croatian cohort, consisting of 130 breast cancer cases and 101 controls ( [88](#B88) ).

## Conclusion

Although TLR9 is widely expressed in breast cancers, it appears that tumor TLR9 expression has prognostic significance only in TNBC. Especially, TNBC patients that have low tumor TLR9 expression upon diagnosis have a significantly shortened disease-specific survival, as compared with TNBC patients that have high tumor TLR9 expression. These findings, however, need to be repeated in larger and more diverse patient populations. TNBC tumors are typically hypoxic and low oxygen concentrations up-regulate TLR9 expression in TNBC cells in pre-clinical models. Understanding why TLR9 expression levels remain low in some TNBC tumors in the hypoxic tumor microenvironment might reveal novel therapeutic opportunities. It has been demonstrated recently that viral oncoproteins down-regulate TLR9 expression in various cancer tissues. Although breast cancer is not currently considered to have viral etiology, various viruses known to be capable of down-regulating TLR9 expression have also been detected in breast cancers. The contribution of these viral infections to low tumor TLR9 status in TNBC should therefore be addressed in future studies. Finally, the mechanisms how the lack of tumor TLR9 expression results in poor prognosis are unknown. Studies from pre-clinical TNBC models suggest that tumor TLR9 expression might affect tumor immunophenotype or be required for chemotherapy-induced anti-tumor immune response. If this is the case, then patients with low-TLR9–TNBC tumors might benefit from anti-cancer immune therapy. The specificity of the immune therapy requires, however, a clear understanding of how TLR9 expression affects tumor immunity. Synthetic TLR9 agonists, CpG–ODNs have demonstrated promising direct and immune system-mediated anti-cancer effects against breast cancer in pre-clinical models but they have not been studied in clinical breast cancer trials. It is clear that synthetic CpG–ODNs induce cancer-cell invasion *in vitro* . Whether this finding is relevant for the clinical situation, where such agonists are given in order to boost the anti-tumor immune response, remains to be resolved. Finally, aiming to increase tumor TLR9 expression prior to chemotherapy should be considered a therapeutic opportunity in the TNBC patients that have low tumor TLR9.

## Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Acknowledgments

Dr. Johanna Tuomela (University of Turku, Finland) and Dr. Kevin Harris (University of Alabama at Birmingham, AL, USA) are kindly acknowledged for carefully reviewing the manuscript.

## References

1. Hemmi H, Takeuchi O, Kawai T, Kaisho T, Sato S, Sanjo H, et al. A toll-like receptor recognizes bacterial DNA. *Nature* (2000)408 : 740–5. doi: 10. 1038/35047123

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11130078) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11130078) | [CrossRef Full Text](http://dx.doi.org/10.1038/35047123)

2. Akira S, Hemmi H. Recognition of pathogen-associated molecular patterns by TLR family. *Immunol Lett* (2003)85 : 85–95. doi: 10. 1016/S0165-2478(02)00228-6

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12527213) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12527213) | [CrossRef Full Text](http://dx.doi.org/10.1016/S0165-2478(02)00228-6)

3. Bamboat ZM, Balachandran VP, Ocuin LM, Obaid H, Plitas G, DeMatteo RP. Toll-like receptor 9 inhibition confers protection from liver ischemia-reperfusion injury. *Hepatology* (2010)51 : 621–32. doi: 10. 1002/hep. 23365

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19902481) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=19902481) | [CrossRef Full Text](http://dx.doi.org/10.1002/hep.23365)

4. Rifkin IR, Leadbetter EA, Busconi L, Viglianti G, Marshak-Rothstein A. Toll-like receptors, endogenous ligands, and systemic autoimmune disease. *Immunol Rev* (2005)204 : 27–42. doi: 10. 1111/j. 0105-2896. 2005. 00239. x

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15790348) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15790348) | [CrossRef Full Text](http://dx.doi.org/10.1111/j.0105-2896.2005.00239.x)

5. Barrat FJ, Meeker T, Gregorio J, Chan JH, Uematsu S, Akira S, et al. Nucleic acids of mammalian origin can act as endogenous ligands for toll-like receptors and may promote systemic lupus erythematosus. *J Exp Med* (2005)202 : 1131–9. doi: 10. 1084/jem. 20050914

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16230478) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16230478) | [CrossRef Full Text](http://dx.doi.org/10.1084/jem.20050914)

6. Bauer S, Kirschning CJ, Häcker H, Redecke V, Hausmann S, Akira S, et al. Human TLR9 confers responsiveness to bacterial DNA via species-specific CpG motif recognition. *Proc Natl Acad Sci U S A* (2001)98 : 9237–42. doi: 10. 1073/pnas. 161293498

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11470918) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11470918) | [CrossRef Full Text](http://dx.doi.org/10.1073/pnas.161293498)

7. Suwarti S, Yamazaki T, Svetlana C, Hanagata N. Recognition of CpG oligodeoxynucleotides by human toll-like receptor 9 and subsequent cytokine induction. *Biochem Biophys Res Commun* (2013)430 : 1234–9. doi: 10. 1016/j. bbrc. 2012. 12. 068

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23266611) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23266611) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.bbrc.2012.12.068)

8. Haas T, Schmitz F, Heit A, Wagner H. Sequence independent interferon-alpha induction by multimerized phosphodiester DNA depends on spatial regulation of toll-like receptor-9 activation in plasmacytoid dendritic cells. *Immunology* (2009)126 : 290–8. doi: 10. 1111/j. 1365-2567. 2008. 02897. x

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19019086) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=19019086) | [CrossRef Full Text](http://dx.doi.org/10.1111/j.1365-2567.2008.02897.x)

9. Leifer CA, Kennedy MN, Mazzoni A, Lee C, Kruhlak MJ, Segal DM. TLR9 is localized in the endoplasmic reticulum prior to stimulation. *J Immunol* (2004)173 : 1179–83. doi: 10. 4049/jimmunol. 173. 2. 1179

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15240708) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15240708) | [CrossRef Full Text](http://dx.doi.org/10.4049/jimmunol.173.2.1179)

10. Hidmark A, von Saint Paul A, Dalpke AH. Cutting edge: TLR13 is a receptor for bacterial RNA. *J Immunol* (2012)189 (6): 2717–21. doi: 10. 4049/jimmunol. 1200898

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22896636) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=22896636) | [CrossRef Full Text](http://dx.doi.org/10.4049/jimmunol.1200898)

11. Latz E, Schoenemeyer A, Visintin A, Fitzgerald KA, Monks BG, Knetter CF, et al. TLR9 signals after translocating from the ER to CpG DNA in the lysosome. *Nat Immunol* (2004)5 : 190–8. doi: 10. 1038/ni1028

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=14716310) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=14716310) | [CrossRef Full Text](http://dx.doi.org/10.1038/ni1028)

12. Bauer S. Toll-like receptor 9 processing: the key event in toll-like receptor 9 activation? *Immunol Lett* (2013)149 : 85–7. doi: 10. 1016/j. imlet. 2012. 11. 003

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23183093) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23183093) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.imlet.2012.11.003)

13. Blasius AL, Beutler B. Intracellular toll-like receptors. *Immunity* (2010)32 : 305–15. doi: 10. 1016/j. immuni. 2010. 03. 012

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20346772) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20346772) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.immuni.2010.03.012)

14. Gilliet M, Cao W, Liu YJ. Plasmacytoid dendritic cells: sensing nucleic acids in viral infection and autoimmune diseases. *Nat Rev Immunol* (2008)8 : 594–606. doi: 10. 1038/nri2358

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18641647) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=18641647) | [CrossRef Full Text](http://dx.doi.org/10.1038/nri2358)

15. Akira S, Takeda K, Kaisho T. Toll-like receptors: critical proteins linking innate and acquired immunity. *Nat Immunol* (2001)2 : 675–80. doi: 10. 1038/90609

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11477402) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11477402) | [CrossRef Full Text](http://dx.doi.org/10.1038/90609)

16. Hoque R, Malik AF, Gorelick F, Mehal WZ. Sterile inflammatory response in acute pancreatitis. *Pancreas* (2012)41 : 353–7. doi: 10. 1097/MPA. 0b013e3182321500

[CrossRef Full Text](http://dx.doi.org/10.1097/MPA.0b013e3182321500)

17. Huang H, Evankovich J, Yan W, Nace G, Zhang L, Ross M, et al. Endogenous histones function as alarmins in sterile inflammatory liver injury through toll-like receptor 9 in mice. *Hepatology* (2011)54 : 999–1008. doi: 10. 1002/hep. 24501

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21721026) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=21721026) | [CrossRef Full Text](http://dx.doi.org/10.1002/hep.24501)

18. Imaeda AB, Watanabe A, Sohail MA, Mahmood S, Mohamadnejad M, Sutterwala FS, et al. Acetaminophen-induced hepatotoxicity in mice is dependent on Tlr9 and the Nalp3 inflammasome. *J Clin Invest* (2009)119 : 305–14. doi: 10. 1172/JCI35958

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19164858) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=19164858) | [CrossRef Full Text](http://dx.doi.org/10.1172/JCI35958)

19. Kono H, Rock KL. How dying cells alert the immune system to danger. *Nat Rev Immunol* (2008)8 : 279–89. doi: 10. 1038/nri2215

[CrossRef Full Text](http://dx.doi.org/10.1038/nri2215)

20. Coban C, Ishii KJ, Kawai T, Hemmi H, Sato S, Uematsu S, et al. Toll-like receptor 9 mediates innate immune activation by the malaria pigment hemozoin. *J Exp Med* (2005)201 : 19–25. doi: 10. 1084/jem. 20041836

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15630134) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15630134) | [CrossRef Full Text](http://dx.doi.org/10.1084/jem.20041836)

21. Parroche P, Lauw FN, Goutagny N, Latz E, Monks BG, Visintin A, et al. Malaria hemozoin is immunologically inert but radically enhances innate responses by presenting malaria DNA to toll-like receptor 9. *Proc Natl Acad Sci U S A* (2007)104 : 1919–24. doi: 10. 1073/pnas. 0608745104

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17261807) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17261807) | [CrossRef Full Text](http://dx.doi.org/10.1073/pnas.0608745104)

22. Wagner H. Hemozoin: malaria’s “ built-in” adjuvant and TLR9 agonist. *Cell Host Microbe* (2010)7 : 5–6. doi: 10. 1016/j. chom. 2010. 01. 002

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20114022) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20114022) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.chom.2010.01.002)

23. Rigby RE, Webb LM, Mackenzie KJ, Li Y, Leitch A, Reijns MA, et al. RNA: DNA hybrids are a novel molecular pattern sensed by TLR9. *EMBO J* (2014)33 : 542–58. doi: 10. 1002/embj. 201386117

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24514026) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24514026) | [CrossRef Full Text](http://dx.doi.org/10.1002/embj.201386117)

24. Merrell MA, Ilvesaro JM, Lehtonen N, Sorsa T, Gehrs B, Rosenthal E, et al. Toll-like receptor 9 agonists promote cellular invasion by increasing matrix metalloproteinase activity. *Mol Cancer Res* (2006)4 : 437–47. doi: 10. 1158/1541-7786. MCR-06-0007

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16849519) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16849519) | [CrossRef Full Text](http://dx.doi.org/10.1158/1541-7786.MCR-06-0007)

25. Armogida SA, Yannaras NM, Melton AL, Srivastava MD. Identification and quantification of innate immune system mediators in human breast milk. *Allergy Asthma Proc* (2004)25 : 297–304.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15603202) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15603202)

26. Berger R, Fiegl H, Goebel G, Obexer P, Ausserlechner M, Doppler W, et al. Toll-like receptor 9 expression in breast and ovarian cancer is associated with poorly differentiated tumors. *Cancer Sci* (2010)101 : 1059–66. doi: 10. 1111/j. 1349-7006. 2010. 01491. x

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20156214) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20156214) | [CrossRef Full Text](http://dx.doi.org/10.1111/j.1349-7006.2010.01491.x)

27. Väisänen MR, Väisänen T, Jukkola-Vuorinen A, Vuopala KS, Desmond R, Selander KS, et al. Expression of toll-like receptor-9 is increased in poorly differentiated prostate tumors. *Prostate* (2010)70 : 817–24. doi: 10. 1002/pros. 21115

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20054821) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20054821) | [CrossRef Full Text](http://dx.doi.org/10.1002/pros.21115)

28. Ilvesaro JM, Merrell MA, Swain TM, Davidson J, Zayzafoon M, Harris KW, et al. Toll like receptor-9 agonists stimulate prostate cancer invasion in vitro. *Prostate* (2007)67 : 774–81. doi: 10. 1002/pros. 20562

[CrossRef Full Text](http://dx.doi.org/10.1002/pros.20562)

29. Jukkola-Vuorinen A, Rahko E, Vuopala KS, Desmond R, Lehenkari PP, Harris KW, et al. Toll-like receptor-9 expression is inversely correlated with estrogen receptor status in breast cancer. *J Innate Immun* (2008)1 : 59–68. doi: 10. 1159/000151602

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20375566) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20375566) | [CrossRef Full Text](http://dx.doi.org/10.1159/000151602)

30. Ronkainen H, Hirvikoski P, Kauppila S, Vuopala KS, Paavonen TK, Selander KS, et al. Absent toll-like receptor-9 expression predicts poor prognosis in renal cell carcinoma. *J Exp Clin Cancer Res* (2011)30 : 84. doi: 10. 1186/1756-9966-30-84

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21929816) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=21929816) | [CrossRef Full Text](http://dx.doi.org/10.1186/1756-9966-30-84)

31. Takala H, Kauppila JH, Soini Y, Selander KS, Vuopala KS, Lehenkari PP, et al. Toll-like receptor 9 is a novel biomarker for esophageal squamous cell dysplasia and squamous cell carcinoma progression. *J Innate Immun* (2011)3 : 631–8. doi: 10. 1159/000329115

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21876325) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=21876325) | [CrossRef Full Text](http://dx.doi.org/10.1159/000329115)

32. Tuomela J, Sandholm J, Karihtala P, Ilvesaro J, Vuopala KS, Kauppila JH, et al. Low TLR9 expression defines an aggressive subtype of triple-negative breast cancer. *Breast Cancer Res Treat* (2012)135 : 481–93. doi: 10. 1007/s10549-012-2181-7

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22847512) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=22847512) | [CrossRef Full Text](http://dx.doi.org/10.1007/s10549-012-2181-7)

33. Väisänen MR, Jukkola-Vuorinen A, Vuopala KS, Selander KS, Vaarala MH. Expression of toll-like receptor-9 is associated with poor progression-free survival in prostate cancer. *Oncol Lett* (2013)5 : 1659–63.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23761830) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23761830)

34. González-Reyes S, Marín L, González L, González LO, del CasarJM, Lamelas ML, et al. Study of TLR3, TLR4 and TLR9 in breast carcinomas and their association with metastasis. *BMC Cancer* (2010)10 : 665. doi: 10. 1186/1471-2407-10-665

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21129170) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=21129170) | [CrossRef Full Text](http://dx.doi.org/10.1186/1471-2407-10-665)

35. Ilvesaro JM, Merrell MA, Li L, Wakchoure S, Graves D, Brooks S, et al. Toll-like receptor 9 mediates CpG oligonucleotide-induced cellular invasion. *Mol Cancer Res* (2008)6 : 1534–43. doi: 10. 1158/1541-7786. MCR-07-2005

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18922969) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=18922969) | [CrossRef Full Text](http://dx.doi.org/10.1158/1541-7786.MCR-07-2005)

36. Sandholm J, Kauppila JH, Pressey C, Tuomela J, Jukkola-Vuorinen A, Vaarala M, et al. Estrogen receptor-alpha and sex steroid hormones regulate toll-like receptor-9 expression and invasive function in human breast cancer cells. *Breast Cancer Res Treat* (2012)132 : 411–9. doi: 10. 1007/s10549-011-1590-3

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21607583) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=21607583) | [CrossRef Full Text](http://dx.doi.org/10.1007/s10549-011-1590-3)

37. McKelvey KJ, Highton J, Hessian PA. Cell-specific expression of TLR9 isoforms in inflammation. *J Autoimmun* (2011)36 (1): 76–86. doi: 10. 1016/j. jaut. 2010. 11. 001

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21115235) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=21115235) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.jaut.2010.11.001)

38. Wang C, Cao S, Yan Y, Ying Q, Jiang T, Xu K, et al. TLR9 expression in glioma tissues correlated to glioma progression and the prognosis of GBM patients. *BMC Cancer* (2010)10 : 415. doi: 10. 1186/1471-2407-10-415

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20696081) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20696081) | [CrossRef Full Text](http://dx.doi.org/10.1186/1471-2407-10-415)

39. Kauppila JH, Takala H, Selander KS, Lehenkari PP, Saarnio J, Karttunen TJ. Increased toll-like receptor 9 expression indicates adverse prognosis in oesophageal adenocarcinoma. *Histopathology* (2011)59 : 643–9. doi: 10. 1111/j. 1365-2559. 2011. 03991. x

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22014045) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=22014045) | [CrossRef Full Text](http://dx.doi.org/10.1111/j.1365-2559.2011.03991.x)

40. Coch C, Busch N, Wimmenauer V, Hartmann E, Janke M, Abdel-Mottaleb MM, et al. Higher activation of TLR9 in plasmacytoid dendritic cells by microbial DNA compared with self-DNA based on CpG-specific recognition of phosphodiester DNA. *J Leukoc Biol* (2009)86 : 663–70. doi: 10. 1189/jlb. 0509314

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19620253) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=19620253) | [CrossRef Full Text](http://dx.doi.org/10.1189/jlb.0509314)

41. Qiao B, Li B, Yang X, Zhang H, Chu Y, Wang Y, et al. Specific siRNA downregulated TLR9 and altered cytokine expression pattern in macrophage after CpG DNA stimulation. *Cell Mol Immunol* (2005)2 : 130–5.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16191419) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16191419)

42. Lahoud MH, Ahmet F, Zhang JG, Meuter S, Policheni AN, Kitsoulis S, et al. DEC-205 is a cell surface receptor for CpG oligonucleotides. *Proc Natl Acad Sci U S A* (2012)109 : 16270–5. doi: 10. 1073/pnas. 1208796109

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22988114) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=22988114) | [CrossRef Full Text](http://dx.doi.org/10.1073/pnas.1208796109)

43. Kauppila JH, Karttunen TJ, Saarnio J, Nyberg P, Salo T, Graves DE, et al. Short DNA sequences and bacterial DNA induce esophageal, gastric, and colorectal cancer cell invasion. *APMIS* (2013)121 : 511–22. doi: 10. 1111/apm. 12016

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23082743) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23082743) | [CrossRef Full Text](http://dx.doi.org/10.1111/apm.12016)

44. Nurmenniemi S, Kuvaja P, Lehtonen S, Tiuraniemi S, Alahuhta I, Mattila RK, et al. Toll-like receptor 9 ligands enhance mesenchymal stem cell invasion and expression of matrix metalloprotease-13. *Exp Cell Res* (2010)316 : 2676–82. doi: 10. 1016/j. yexcr. 2010. 05. 024

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20553713) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20553713) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.yexcr.2010.05.024)

45. Jozsef L, Khreiss T, El Kebir D, Filep JG. Activation of TLR-9 induces IL-8 secretion through peroxynitrite signaling in human neutrophils. *J Immunol* (2006)176 : 1195–202. doi: 10. 4049/jimmunol. 176. 2. 1195

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16394009) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16394009) | [CrossRef Full Text](http://dx.doi.org/10.4049/jimmunol.176.2.1195)

46. Peter M, Bode K, Lipford GB, Eberle F, Heeg K, Dalpke AH. Characterization of suppressive oligodeoxynucleotides that inhibit toll-like receptor-9-mediated activation of innate immunity. *Immunology* (2008)123 : 118–28. doi: 10. 1111/j. 1365-2567. 2007. 02718. x

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17961163) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17961163) | [CrossRef Full Text](http://dx.doi.org/10.1111/j.1365-2567.2007.02718.x)

47. Tuomela J, Sandholm J, Kaakinen M, Patel A, Kauppila JH, Ilvesaro J, et al. DNA from dead cancer cells induces TLR9-mediated invasion and inflammation in living cancer cells. *Breast Cancer Res Treat* (2013)142 : 477–87. doi: 10. 1007/s10549-013-2762-0

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24212717) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24212717) | [CrossRef Full Text](http://dx.doi.org/10.1007/s10549-013-2762-0)

48. Lande R, Gregorio J, Facchinetti V, Chatterjee B, Wang YH, Homey B, et al. Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide. *Nature* (2007)449 : 564–9. doi: 10. 1038/nature06116

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17873860) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17873860) | [CrossRef Full Text](http://dx.doi.org/10.1038/nature06116)

49. Weber G, Chamorro CI, Granath F, Liljegren A, Zreika S, Saidak Z, et al. Human antimicrobial protein hCAP18/LL-37 promotes a metastatic phenotype in breast cancer. *Breast Cancer Res* (2009)11 : R6. doi: 10. 1186/bcr2221

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19183447) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=19183447) | [CrossRef Full Text](http://dx.doi.org/10.1186/bcr2221)

50. Heilborn JD, Nilsson MF, Jimenez CI, Sandstedt B, Borregaard N, Tham E, et al. Antimicrobial protein hCAP18/LL-37 is highly expressed in breast cancer and is a putative growth factor for epithelial cells. *Int J Cancer* (2005)114 : 713–9. doi: 10. 1002/ijc. 20795

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=15609314) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=15609314) | [CrossRef Full Text](http://dx.doi.org/10.1002/ijc.20795)

51. Kuhlicke J, Frick JS, Morote-Garcia JC, Rosenberger P, Eltzschig HK. Hypoxia inducible factor (HIF)-1 coordinates induction of toll-like receptors TLR2 and TLR6 during hypoxia. *PLoS One* (2007)2 : e1364. doi: 10. 1371/journal. pone. 0001364

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18159247) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=18159247) | [CrossRef Full Text](http://dx.doi.org/10.1371/journal.pone.0001364)

52. Oka T, Hikoso S, Yamaguchi O, Taneike M, Takeda T, Tamai T, et al. Mitochondrial DNA that escapes from autophagy causes inflammation and heart failure. *Nature* (2012)485 : 251–5. doi: 10. 1038/nature10992

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22535248) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=22535248) | [CrossRef Full Text](http://dx.doi.org/10.1038/nature10992)

53. Sandholm J, Tuomela J, Kauppila JH, Harris KW, Graves D, Selander KS. Hypoxia regulates toll-like receptor-9 expression and invasive function in human brain cancer cells in vitro. *Oncol Lett* (2014)8 (1): 266–74.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24959259) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24959259)

54. De Nardo D, De Nardo CM, Nguyen T, Hamilton JA, Scholz GM. Signaling crosstalk during sequential TLR4 and TLR9 activation amplifies the inflammatory response of mouse macrophages. *J Immunol* (2009)183 : 8110–8. doi: 10. 4049/jimmunol. 0901031

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19923461) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=19923461) | [CrossRef Full Text](http://dx.doi.org/10.4049/jimmunol.0901031)

55. Krieg AM. CpG still rocks! Update on an accidental drug. *Nucleic Acid Ther* (2012)22 : 77–89. doi: 10. 1089/nat. 2012. 0340

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22352814) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=22352814) | [CrossRef Full Text](http://dx.doi.org/10.1089/nat.2012.0340)

56. Xiong Z, Gharagozlou S, Vengco I, Chen W, Ohlfest JR. Effective CpG immunotherapy of breast carcinoma prevents but fails to eradicate established brain metastasis. *Clin Cancer Res* (2008)14 : 5484–93. doi: 10. 1158/1078-0432. CCR-07-4139

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=18765540) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=18765540) | [CrossRef Full Text](http://dx.doi.org/10.1158/1078-0432.CCR-07-4139)

57. Cai Q, Kublo L, Cumberland R, Gooding W, Baar J. Optimized systemic dosing with CpG DNA enhances dendritic cell-mediated rejection of a poorly immunogenic mammary tumor in BALB/c mice. *Clin Transl Sci* (2009)2 : 62–6. doi: 10. 1111/j. 1752-8062. 2008. 00073. x

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20443869) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20443869) | [CrossRef Full Text](http://dx.doi.org/10.1111/j.1752-8062.2008.00073.x)

58. Nava-Parada P, Forni G, Knutson KL, Pease LR, Celis E. Peptide vaccine given with a toll-like receptor agonist is effective for the treatment and prevention of spontaneous breast tumors. *Cancer Res* (2007)67 : 1326–34. doi: 10. 1158/0008-5472. CAN-06-3290

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17283170) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17283170) | [CrossRef Full Text](http://dx.doi.org/10.1158/0008-5472.CAN-06-3290)

59. Wang H, Rayburn ER, Wang W, Kandimalla ER, Agrawal S, Zhang R. Immunomodulatory oligonucleotides as novel therapy for breast cancer: pharmacokinetics, in vitro and in vivo anticancer activity, and potentiation of antibody therapy. *Mol Cancer Ther* (2006)5 : 2106–14. doi: 10. 1158/1535-7163. MCT-06-0158

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=16928832) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=16928832) | [CrossRef Full Text](http://dx.doi.org/10.1158/1535-7163.MCT-06-0158)

60. Yang L, Wu X, Wan M, Yu Y, Yu Y, Wang L. CpG oligodeoxynucleotides with double stem-loops show strong immunostimulatory activity. *Int Immunopharmacol* (2013)15 : 89–96. doi: 10. 1016/j. intimp. 2012. 10. 020

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23142503) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23142503) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.intimp.2012.10.020)

61. Yu D, Zhu FG, Bhagat L, Wang H, Kandimalla ER, Zhang R, et al. Potent CpG oligonucleotides containing phosphodiester linkages: in vitro and in vivo immunostimulatory properties. *Biochem Biophys Res Commun* (2002)297 : 83–90. doi: 10. 1016/S0006-291X(02)02127-7

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=12220512) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=12220512) | [CrossRef Full Text](http://dx.doi.org/10.1016/S0006-291X(02)02127-7)

62. Hurtado P, Peh CA. LL-37 promotes rapid sensing of CpG oligodeoxynucleotides by B lymphocytes and plasmacytoid dendritic cells. *J Immunol* (2010)184 : 1425–35. doi: 10. 4049/jimmunol. 0902305

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20042575) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20042575) | [CrossRef Full Text](http://dx.doi.org/10.4049/jimmunol.0902305)

63. de la Cruz-Merino L, Barco-Sánchez A, Henao Carrasco F, Nogales Fernández E, Vallejo Benítez A, Brugal Molina J, et al. New insights into the role of the immune microenvironment in breast carcinoma. *Clin Dev Immunol* (2013)2013 : 785317. doi: 10. 1155/2013/785317

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23861693) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23861693) | [CrossRef Full Text](http://dx.doi.org/10.1155/2013/785317)

64. Hasan UA, Bates E, Takeshita F, Biliato A, Accardi R, Bouvard V, et al. TLR9 expression and function is abolished by the cervical cancer-associated human papillomavirus type 16. *J Immunol* (2007)178 : 3186–97. doi: 10. 4049/jimmunol. 178. 5. 3186

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=17312167) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=17312167) | [CrossRef Full Text](http://dx.doi.org/10.4049/jimmunol.178.5.3186)

65. Fathallah I, Parroche P, Gruffat H, Zannetti C, Johansson H, Yue J, et al. EBV latent membrane protein 1 is a negative regulator of TLR9. *J Immunol* (2010)185 : 6439–47. doi: 10. 4049/jimmunol. 0903459

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20980631) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20980631) | [CrossRef Full Text](http://dx.doi.org/10.4049/jimmunol.0903459)

66. Vincent IE, Zannetti C, Lucifora J, Norder H, Protzer U, Hainaut P, et al. Hepatitis B virus impairs TLR9 expression and function in plasmacytoid dendritic cells. *PLoS One* (2011)6 : e26315. doi: 10. 1371/journal. pone. 0026315

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22046272) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=22046272) | [CrossRef Full Text](http://dx.doi.org/10.1371/journal.pone.0026315)

67. Sajadi SM, Mirzaei V, Hassanshahi G, Khorramdelazad H, Daredor HY, Hosseini SM, et al. Decreased expressions of toll-like receptor 9 and its signaling molecules in chronic hepatitis B virus-infected patients. *Arch Pathol Lab Med* (2013)137 : 1674–9. doi: 10. 5858/arpa. 2012-0415-OA

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24168509) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24168509) | [CrossRef Full Text](http://dx.doi.org/10.5858/arpa.2012-0415-OA)

68. Shahzad N, Shuda M, Gheit T, Kwun HJ, Cornet I, Saidj D, et al. The T antigen locus of Merkel cell polyomavirus downregulates human toll-like receptor 9 expression. *J Virol* (2013)87 : 13009–19. doi: 10. 1128/JVI. 01786-13

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24067965) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24067965) | [CrossRef Full Text](http://dx.doi.org/10.1128/JVI.01786-13)

69. Hasan UA, Zannetti C, Parroche P, Goutagny N, Malfroy M, Roblot G, et al. The human papillomavirus type 16 E7 oncoprotein induces a transcriptional repressor complex on the toll-like receptor 9 promoter. *J Exp Med* (2013)210 : 1369–87. doi: 10. 1084/jem. 20122394

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23752229) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23752229) | [CrossRef Full Text](http://dx.doi.org/10.1084/jem.20122394)

70. van Gent M, Griffin BD, Berkhoff EG, van Leeuwen D, Boer IG, Buisson M, et al. EBV lytic-phase protein BGLF5 contributes to TLR9 downregulation during productive infection. *J Immunol* (2011)186 : 1694–702. doi: 10. 4049/jimmunol. 0903120

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21191071) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=21191071) | [CrossRef Full Text](http://dx.doi.org/10.4049/jimmunol.0903120)

71. Xu N, Yao HP, Lv GC, Chen Z. Downregulation of TLR7/9 leads to deficient production of IFN-alpha from plasmacytoid dendritic cells in chronic hepatitis B. *Inflamm Res* (2012)61 : 997–1004. doi: 10. 1007/s00011-012-0493-z

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22684144) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=22684144) | [CrossRef Full Text](http://dx.doi.org/10.1007/s00011-012-0493-z)

72. Hasimu A, Ge L, Li QZ, Zhang RP, Guo X. Expressions of toll-like receptors 3, 4, 7, and 9 in cervical lesions and their correlation with HPV16 infection in Uighur women. *Chin J Cancer* (2011)30 : 344–50. doi: 10. 5732/cjc. 010. 10456

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=21527067) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=21527067) | [CrossRef Full Text](http://dx.doi.org/10.5732/cjc.010.10456)

73. Lagunes-Servin H, Torres J, Maldonado-Bernal C, Pérez-Rodríguez M, Huerta-Yépez S, Madrazo de la Garza A, et al. Toll-like receptors and cytokines are upregulated during Helicobacter pylori infection in children. *Helicobacter* (2013)18 : 423–32. doi: 10. 1111/hel. 12067

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23869400) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23869400) | [CrossRef Full Text](http://dx.doi.org/10.1111/hel.12067)

74. Buehring GC, Shen HM, Jensen HM, Choi KY, Sun D, Nuovo G. Bovine leukemia virus DNA in human breast tissue. *Emerg Infect Dis* (2014)20 : 772–82. doi: 10. 3201/eid2005. 131298

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24750974) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24750974) | [CrossRef Full Text](http://dx.doi.org/10.3201/eid2005.131298)

75. Lv YR, Wang JL, Zhang K, Gao HD, Sun JZ, Gong YY, et al. Human papilloma viruses (HPVs) no co-existence in breast cancer and cervical cells in the same patient. *Chin J Physiol* (2014)57 (2): 105–6. doi: 10. 4077/CJP. 2014. BAC207

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24694200) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24694200) | [CrossRef Full Text](http://dx.doi.org/10.4077/CJP.2014.BAC207)

76. Manzouri L, Salehi R, Shariatpanahi S, Rezaie P. Prevalence of human papilloma virus among women with breast cancer since 2005-2009 in Isfahan. *Adv Biomed Res* (2014)3 : 75. doi: 10. 4103/2277-9175. 125873

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24627883) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24627883) | [CrossRef Full Text](http://dx.doi.org/10.4103/2277-9175.125873)

77. Alibek K, Kakpenova A, Mussabekova A, Sypabekova M, Karatayeva N. Role of viruses in the development of breast cancer. *Infect Agent Cancer* (2013)8 : 32. doi: 10. 1186/1750-9378-8-32

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24138789) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24138789) | [CrossRef Full Text](http://dx.doi.org/10.1186/1750-9378-8-32)

78. Kim SY, Choi YJ, Joung SM, Lee BH, Jung YS, Lee JY. Hypoxic stress up-regulates the expression of toll-like receptor 4 in macrophages via hypoxia-inducible factor. *Immunology* (2010)129 : 516–24. doi: 10. 1111/j. 1365-2567. 2009. 03203. x

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=20002786) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=20002786) | [CrossRef Full Text](http://dx.doi.org/10.1111/j.1365-2567.2009.03203.x)

79. Piccolo S, Enzo E, Montagner M. p63, Sharp1, and HIFs: master regulators of metastasis in triple-negative breast cancer. *Cancer Res* (2013)73 : 4978–81. doi: 10. 1158/0008-5472. CAN-13-0962

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23913939) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23913939) | [CrossRef Full Text](http://dx.doi.org/10.1158/0008-5472.CAN-13-0962)

80. Silver AC, Arjona A, Walker WE, Fikrig E. The circadian clock controls toll-like receptor 9-mediated innate and adaptive immunity. *Immunity* (2012)36 : 251–61. doi: 10. 1016/j. immuni. 2011. 12. 017

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=22342842) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=22342842) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.immuni.2011.12.017)

81. Fioretti FM, Sita-Lumsden A, Bevan CL, Brooke G. Revising the role of the androgen receptor in breast cancer. *J Mol Endocrinol* (2014)52 (3): R257–65. doi: 10. 1530/JME-14-0030

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24740738) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24740738) | [CrossRef Full Text](http://dx.doi.org/10.1530/JME-14-0030)

82. Du X, Poltorak A, Wei Y, Beutler B. Three novel mammalian toll-like receptors: gene structure, expression, and evolution. *Eur Cytokine Netw* (2000)11 : 362–71.

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=11022119) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=11022119)

83. Torres-García D, Cruz-Lagunas A, García-Sancho Figueroa MC, Fernández-Plata R, Baez-Saldaña R, Mendoza-Milla C, et al. Variants in toll-like receptor 9 gene influence susceptibility to tuberculosis in a Mexican population. *J Transl Med* (2013)11 : 220. doi: 10. 1186/1479-5876-11-220

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24053111) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24053111) | [CrossRef Full Text](http://dx.doi.org/10.1186/1479-5876-11-220)

84. Zhang J, Zhu Q, Meng F, Lei H, Zhao Y. Association study of TLR-9 polymorphisms and systemic lupus erythematosus in northern Chinese Han population. *Gene* (2014)533 : 385–8. doi: 10. 1016/j. gene. 2013. 08. 051

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24004541) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24004541) | [CrossRef Full Text](http://dx.doi.org/10.1016/j.gene.2013.08.051)

85. Laska MJ, Troldborg A, Hansen B, Stengaard-Pedersen K, Junker P, Nexø BA, et al. Polymorphisms within toll-like receptors are associated with systemic lupus erythematosus in a cohort of Danish females. *Rheumatology (Oxford)* (2014)53 : 48–55. doi: 10. 1093/rheumatology/ket316

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=24064706) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=24064706) | [CrossRef Full Text](http://dx.doi.org/10.1093/rheumatology/ket316)

86. Wang X, Xue L, Yang Y, Xu L, Zhang G. TLR9 promoter polymorphism is associated with both an increased susceptibility to gastric carcinoma and poor prognosis. *PLoS One* (2013)8 : e65731. doi: 10. 1371/journal. pone. 0065731

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=23776537) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=23776537) | [CrossRef Full Text](http://dx.doi.org/10.1371/journal.pone.0065731)

87. Resler AJ, Malone KE, Johnson LG, Malkki M, Petersdorf EW, McKnight B, et al. Genetic variation in TLR or NFkappaB pathways and the risk of breast cancer: a case-control study. *BMC Cancer* (2013)13 : 219. doi: 10. 1186/1471-2407-13-219

[CrossRef Full Text](http://dx.doi.org/10.1186/1471-2407-13-219)

88. Etokebe GE, Knezevic J, Petricevic B, Pavelic J, Vrbanec D, Dembic Z. Single-nucleotide polymorphisms in genes encoding toll-like receptor -2, -3, -4, and -9 in case-control study with breast cancer. *Genet Test Mol Biomarkers* (2009)13 : 729–34. doi: 10. 1089/gtmb. 2009. 0045

[Pubmed Abstract](http://www.ncbi.nlm.nih.gov/sites/entrez?Db=pubmed&Cmd=ShowDetailView&TermToSearch=19810822) | [Pubmed Full Text](http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?db=pubmed&cmd=prlinks&retmode=ref&id=19810822) | [CrossRef Full Text](http://dx.doi.org/10.1089/gtmb.2009.0045)