

BÖLÜM

5

MİKOZİS FUNGOİDES İMМÜNOPATOLOJİSİ

Begüm ÇALIM GÜRBÜZ¹

Itır Ebru ZEMHERİ²

GİRİŞ

Kutanöz T hücreli lenfomalar (KTHL), sistemik lenfomalardan farklı bir kliniğe sahip olan heterojen bir lenfoma grubudur (Vaidya ve ark., 2022). Mikozis fungoides (MF) ise, KTHL içerisinde en sık görülen lenfoma tipidir (Bradford ve ark., 2009).

Başta MF olmak üzere KTHL'in biyolojisini çözümlemek adına pek çok moleküler mekanizma üzerinde çalışılmaktadır. Hem klinik hem patoloji alanında yapılan, yeni nesil sekanslama çalışmaları bilgileri günden güne artırmakta ve tanı, tedavi ve прогноз konusunda yeni gelişmelerin ortaya konabilme potansiyeli yükselmektedir (García-Díaz ve ark., 2021).

KTHL VE MF İMMUNOPATOLOJİSİ TARİHÇESİ

KTHL'in deriye yerleşen olgun T hücrelerinden geliştiği bilinmektedir. MF; sırası ile yama, plak ve tümör evreleri ile ilerlemektedir. Lenf düğümleri, periferik kan ve organ tutulumları ile kötü bir prognoza sahip olabilir (Arulogun ve ark., 2008). KTHL'in lösemik formu olan Sézary sendromu (SS) ise, kanda malign T hücreleri ile prezente olan generalize cilt eritemi ile karakterizedir. MF, SS ve KTHL'in pek çok ortak ve farklı özellikleri bulunmakta olup bu özelliklerin ayrı ayrı bozukluklarla mı ilişkili olduğu, yoksa genetik çeşitlilik ve mikroçevre ile mi ilgili olduğu konusu ise halen belirsizliğini korumaktadır (Liu ve ark., 2022).

¹ Uzm. Dr., Başakşehir Çam ve Sakura Şehir Hastanesi, Patoloji Kliniği, begumcalim@hotmail.com

² Prof. Dr., Sağlık Bilimleri Üniversitesi, Ümraniye Eğitim ve Araştırma Hastanesi, Patoloji Kliniği, ebruzemheri@gmail.com

KTHL'da lenfotoksin α (LT α) araştırılmış ve LT α 'nın hücre sağkalımı, prolifeراسyonu, differansiasyonu ve apopitoz regülasyonu üzerinde etkili olduğu saptanmıştır (Matsumoto ve ark., 2013). Ayrıca, teorik olarak LT α , IL-6 ve VEGF, endotelial hücrelerde artış ile karakterize olan anjiogenezi indükleyerek tümör gelişimi ve yayılmasını artıracak şekilde bildirilmiştir (Lauenborg ve ark., 2015).

SONUÇ

MF hastalığının immunopatolojisi ile ilgili süregelen çalışmalar mevcut olup, günümüz dünyasının bilgi birikiminin de eklenmesiyle oldukça kompleks bir hale gelmeye başlamıştır. MF oluşum süreci ve прогнозuya ilgili pek çok yolak üzerinde çalışılmıştır. Bu yolklara, son yıllarda çoğu tümörde araştırma konusu haline gelmiş mikroçevre de eklenmiştir. Doğası ve kökeni gereği, mikroçevre hücreleri ile ilişkisi her zaman optimal olarak ortaya konamayan MF hastalığı hakkında bu konuda yeni çalışmalarla ihtiyaç duyulmaktadır. Kötü прогноз parametresi olarak kullanılabilen bulgular hakkında çalışmalar türetilirken, bunların daha sağlam temellere oturtulması gereklidir. Bu durum yeni terapötik seçeneklerin geliştirilerek, hastaların tedavi ve takiplerinde bir adım öteye geçilmesine sebep olacaktır.

KAYNAKLAR

- Vaidya T& Badri T. Mycosis Fungoides. [Updated 2022 Apr 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK519572/>
- Bradford, P. T., Devesa, S. S., Anderson, W. F., & Toro, J. R. (2009). Cutaneous lymphoma incidence patterns in the United States: a population-based study of 3884 cases. *Blood*, 113(21), 5064–5073. <https://doi.org/10.1182/blood-2008-10-184168>
- García-Díaz, N., Piris, M. Á., Ortiz-Romero, P. L., & Vaqué, J. P. (2021). Mycosis Fungoides and Sézary Syndrome: An Integrative Review of the Pathophysiology, Molecular Drivers, and Targeted Therapy. *Cancers*, 13(8), 1931. <https://doi.org/10.3390/cancers13081931>
- Arulogun, S. O., Prince, H. M., Ng, J., Lade, S., Ryan, G. F., Blewitt, O., & McCormack, C. (2008). Long-term outcomes of patients with advanced-stage cutaneous T-cell lymphoma and large cell transformation. *Blood*, 112(8), 3082–3087. <https://doi.org/10.1182/blood-2008-05-154609>
- Liu, X., Jin, S., Hu, S., Li, R., Pan, H., Liu, Y., Lai, P., Xu, D., Sun, J., Liu, Z., Gao, Y., Zhao, Y., Liu, F., Xiao, Y., Li, Y., Wen, Y., Chen, Z., Xu, B., Lin, Y., Ran, M., ... Wang, Y.

- (2022). Single-cell transcriptomics links malignant T cells to the tumor immune landscape in cutaneous T cell lymphoma. *Nature communications*, 13(1), 1158. <https://doi.org/10.1038/s41467-022-28799-3>
- Campbell, J. J., Clark, R. A., Watanabe, R., & Kupper, T. S. (2010). Sezary syndrome and mycosis fungoides arise from distinct T-cell subsets: a biologic rationale for their distinct clinical behaviors. *Blood*, 116(5), 767–771. <https://doi.org/10.1182/blood-2009-11-251926>
- Iyer, A., Hennessey, D., O'Keefe, S., Patterson, J., Wang, W., Wong, G. K., & Gniadecki, R. (2020). Branched evolution and genomic intratumor heterogeneity in the pathogenesis of cutaneous T-cell lymphoma. *Blood advances*, 4(11), 2489–2500. <https://doi.org/10.1182/bloodadvances.2020001441>
- Iyer, A., Hennessey, D., O'Keefe, S., Patterson, J., Wang, W., Wong, G. K., & Gniadecki, R. (2019). Skin colonization by circulating neoplastic clones in cutaneous T-cell lymphoma. *Blood*, 134(18), 1517–1527. <https://doi.org/10.1182/blood.2019002516>
- Quaglino, P., Fava, P., Pileri, A., Grandi, V., Sanlorenzo, M., Panasiti, V., Guglielmo, A., Alberti-Violetti, S., Novelli, M., Astrua, C., Rubatto, M., Tonella, L., Berti, E., Pimpinelli, N., Osella Abate, S., Fierro, M. T., Vermeer, M., Scarisbrick, J. J., & Ribero, S. (2021). Phenotypical Markers, Molecular Mutations, and Immune Microenvironment as Targets for New Treatments in Patients with Mycosis Fungoides and/or Sézary Syndrome. *The Journal of investigative dermatology*, 141(3), 484–495. <https://doi.org/10.1016/j.jid.2020.07.026>
- Burnet M. (1957). Cancer: a biological approach. III. Viruses associated with neoplastic conditions. IV. Practical applications. *British medical journal*, 1(5023), 841–847. <https://doi.org/10.1136/bmjj.1.5023.841>
- Dominguez-Villar, M., Gautron, A. S., de Marcken, M., Keller, M. J., & Hafler, D. A. (2015). TLR7 induces anergy in human CD4(+) T cells. *Nature immunology*, 16(1), 118–128. <https://doi.org/10.1038/ni.3036>
- Dinarello C. A. (2007). Historical insights into cytokines. *European journal of immunology*, 37 Suppl 1(Suppl 1), S34–S45. <https://doi.org/10.1002/eji.200737772>
- Sun, J. C., & Lanier, L. L. (2009). Natural killer cells remember: an evolutionary bridge between innate and adaptive immunity? *European journal of immunology*, 39(8), 2059–2064. <https://doi.org/10.1002/eji.200939435>
- Alcover, A., Alarcón, B., & Di Bartolo, V. (2018). Cell Biology of T Cell Receptor Expression and Regulation. *Annual review of immunology*, 36, 103–125. <https://doi.org/10.1146/annurev-immunol-042617-053429>
- Brownlie, R. J., & Zamoyska, R. (2013). T cell receptor signalling networks: branched, diversified and bounded. *Nature reviews. Immunology*, 13(4), 257–269. <https://doi.org/10.1038/nri3403>
- Choi, J., Goh, G., Walradt, T., Hong, B. S., Bunick, C. G., Chen, K., Bjornson, R. D., Maman, Y., Wang, T., Tordoff, J., Carlson, K., Overton, J. D., Liu, K. J., Lewis, J. M., Devine, L., Barbarotta, L., Foss, F. M., Subtil, A., Vonderheid, E. C., Edelson, R. L., ... Lifton, R. P. (2015). Genomic landscape of cutaneous T cell lymphoma. *Nature genetics*, 47(9), 1011–1019. <https://doi.org/10.1038/ng.3356>
- Vaqué, J. P., Gómez-López, G., Monsálvez, V., Varela, I., Martínez, N., Pérez, C., Domínguez, O., Graña, O., Rodríguez-Peralto, J. L., Rodríguez-Pinilla, S. M., González-Vela, C.,

- Rubio-Camarillo, M., Martín-Sánchez, E., Pisano, D. G., Papadavid, E., Papadaki, T., Requena, L., García-Marco, J. A., Méndez, M., Provencio, M., ... Sánchez-Beato, M. (2014). PLCG1 mutations in cutaneous T-cell lymphomas. *Blood*, 123(13), 2034–2043. <https://doi.org/10.1182/blood-2013-05-504308>
- Nguyen, T. N., Kim, L. J., Walters, R. D., Drullinger, L. F., Lively, T. N., Kugel, J. F., & Goodrich, J. A. (2010). The C-terminal region of human NFATc2 binds cJun to synergistically activate interleukin-2 transcription. *Molecular immunology*, 47(14), 2314–2322. <https://doi.org/10.1016/j.molimm.2010.05.287>
- Altman, A., & Kong, K. F. (2016). Protein Kinase C Enzymes in the Hematopoietic and Immune Systems. *Annual review of immunology*, 34, 511–538. <https://doi.org/10.1146/annurev-immunol-041015-055347>
- Fan, Y., Mao, R., & Yang, J. (2013). NF- κ B and STAT3 signaling pathways collaboratively link inflammation to cancer. *Protein & cell*, 4(3), 176–185. <https://doi.org/10.1007/s13238-013-2084-3>
- Yamaoka, K., Saharinen, P., Pesu, M., Holt, V. E., 3rd, Silvennoinen, O., & O’Shea, J. J. (2004). The Janus kinases (Jaks). *Genome biology*, 5(12), 253. <https://doi.org/10.1186/gb-2004-5-12-253>
- Goswami, R., & Kaplan, M. H. (2017). STAT Transcription Factors in T Cell Control of Health and Disease. *International review of cell and molecular biology*, 331, 123–180. <https://doi.org/10.1016/bs.ircmb.2016.09.012>
- Pérez, C., Mondéjar, R., García-Díaz, N., Cereceda, L., León, A., Montes, S., Durán Vian, C., Pérez Paredes, M. G., González-Morán, A., Alegre de Miguel, V., Sanz Anquela, J. M., Frias, J., Limeres, M. A., González, L. M., Martín Dávila, F., Beltrán, M., Mollejo, M., Méndez, J. R., González, M. A., González García, J., ... Piris, M. A. (2020). Advanced-stage mycosis fungoides: role of the signal transducer and activator of transcription 3, nuclear factor- κ B and nuclear factor of activated T cells pathways. *The British journal of dermatology*, 182(1), 147–155. <https://doi.org/10.1111/bjd.18098>
- Calò, V., Migliavacca, M., Bazan, V., Macaluso, M., Buscemi, M., Gebbia, N., & Russo, A. (2003). STAT proteins: from normal control of cellular events to tumorigenesis. *Journal of cellular physiology*, 197(2), 157–168. <https://doi.org/10.1002/jcp.10364>
- Willerslev-Olsen, A., Krejsgaard, T., Lindahl, L. M., Litvinov, I. V., Fredholm, S., Petersen, D. L., Nastasi, C., Gniadecki, R., Mongan, N. P., Sasseville, D., Wasik, M. A., Bonefeld, C. M., Geisler, C., Woetmann, A., Iversen, L., Kilian, M., Koralov, S. B., & Odum, N. (2016). Staphylococcal enterotoxin A (SEA) stimulates STAT3 activation and IL-17 expression in cutaneous T-cell lymphoma. *Blood*, 127(10), 1287–1296. <https://doi.org/10.1182/blood-2015-08-662353>
- Waldmann, T. A., & Chen, J. (2017). Disorders of the JAK/STAT Pathway in T Cell Lymphoma Pathogenesis: Implications for Immunotherapy. *Annual review of immunology*, 35, 533–550. <https://doi.org/10.1146/annurev-immunol-110416-120628>
- Farber, D. L., Yudanin, N. A., & Restifo, N. P. (2014). Human memory T cells: generation, compartmentalization and homeostasis. *Nature reviews. Immunology*, 14(1), 24–35. <https://doi.org/10.1038/nri3567>
- Förster, R., Davalos-Misslitz, A. C., & Rot, A. (2008). CCR7 and its ligands: balancing immunity and tolerance. *Nature reviews. Immunology*, 8(5), 362–371. <https://doi.org/10.1038/nri2297>

- Pileri, A., Guglielmo, A., Grandi, V., Violetti, S. A., Fanoni, D., Fava, P., Agostinelli, C., Berti, E., Quaglino, P., & Pimpinelli, N. (2021). The Microenvironment's Role in Mycosis Fungoides and Sézary Syndrome: From Progression to Therapeutic Implications. *Cells*, 10(10), 2780. <https://doi.org/10.3390/cells10102780>
- Dunn, G. P., Old, L. J., & Schreiber, R. D. (2004). The immunobiology of cancer immuno-surveillance and immuno-editing. *Immunity*, 21(2), 137–148. <https://doi.org/10.1016/j.immuni.2004.07.017>
- Der-Petrosian, M., Valencak, J., Jonak, C., Klosner, G., Dani, T., Müllauer, L., Pehamberger, H., Knobler, R., & Trautinger, F. (2011). Dermal infiltrates of cutaneous T-cell lymphomas with epidermotropism but not other cutaneous lymphomas are abundant with langerin dendritic cells. *Journal of the European Academy of Dermatology and Venereology : JEADV*, 25(8), 922–927. <https://doi.org/10.1111/j.1468-3083.2010.03882.x>
- Schwingenschäckl, P., Obermoser, G., Nguyen, V. A., Fritsch, P., Sepp, N., & Romani, N. (2012). Distribution and maturation of skin dendritic cell subsets in two forms of cutaneous T-cell lymphoma: mycosis fungoides and Sézary syndrome. *Acta dermato-venereologica*, 92(3), 269–275. <https://doi.org/10.2340/00015555-1220>
- Argyropoulos, K. V., Pulitzer, M., Perez, S., Korkolopoulou, P., Angelopoulou, M., Baxevanis, C., Palomba, M. L., & Siakantaris, M. (2020). Tumor-infiltrating and circulating granulocytic myeloid-derived suppressor cells correlate with disease activity and adverse clinical outcomes in mycosis fungoides. *Clinical & translational oncology : official publication of the Federation of Spanish Oncology Societies and of the National Cancer Institute of Mexico*, 22(7), 1059–1066. <https://doi.org/10.1007/s12094-019-02231-7>
- Sarvaria, A., Madrigal, J. A., & Saudemont, A. (2017). B cell regulation in cancer and anti-tumor immunity. *Cellular & molecular immunology*, 14(8), 662–674. <https://doi.org/10.1038/cmi.2017.35>
- Akatsuka, T., Miyagaki, T., Nakajima, R., Kamijo, H., Oka, T., Takahashi, N., Suga, H., Yoshizaki, A., Asano, Y., Sugaya, M., & Sato, S. (2018). Decreased IL-10-producing regulatory B cells in patients with advanced mycosis fungoides. *European journal of dermatology : EJD*, 28(3), 314–319. <https://doi.org/10.1684/ejd.2018.3319>
- Nikolaou, V., Iliakis, T., Marinos, L., Voudouri, D., Sidiropoulou, P., Rigopoulos, D., & Stratigos, A. J. (2020). Another window into tumor microenvironment: a case of B-cell rich folliculotropic mycosis fungoides responding to rituximab. *The Australasian journal of dermatology*, 61(2), e226–e228. <https://doi.org/10.1111/ajd.13217>
- Tschetter, A. J., Zafar, F., Moye, M. S., Ghahramani, G. K., Swick, B. L., Link, B. K., & Liu, V. (2020). CD20+ cutaneous T-cell lymphoma with phenotypic shift after treatment with rituximab: Case report and review of the literature. *JAAD case reports*, 6(4), 308–310. <https://doi.org/10.1016/j.jdcr.2020.01.015>
- Berger, C. L., Tigelaar, R., Cohen, J., Mariwalla, K., Trinh, J., Wang, N., & Edelson, R. L. (2005). Cutaneous T-cell lymphoma: malignant proliferation of T-regulatory cells. *Blood*, 105(4), 1640–1647. <https://doi.org/10.1182/blood-2004-06-2181>
- Hallermann, C., Niermann, C., & Schulze, H. J. (2007). Regulatory T-cell phenotype in association with large cell transformation of mycosis fungoides. *European journal of haematology*, 78(3), 260–263. <https://doi.org/10.1111/j.1600-0609.2006.00809.x>

- Wada, D. A., Wilcox, R. A., Weenig, R. H., & Gibson, L. E. (2010). Paucity of intraepidermal FoxP3-positive T cells in cutaneous T-cell lymphoma in contrast with spongiotic and lichenoid dermatitis. *Journal of cutaneous pathology*, 37(5), 535–541. <https://doi.org/10.1111/j.1600-0560.2009.01381.x>
- Gjerdrum, L. M., Woetmann, A., Odum, N., Burton, C. M., Rossen, K., Skovgaard, G. L., Ryder, L. P., & Ralfkiaer, E. (2007). FOXP3+ regulatory T cells in cutaneous T-cell lymphomas: association with disease stage and survival. *Leukemia*, 21(12), 2512–2518. <https://doi.org/10.1038/sj.leu.2404913>
- Querfeld, C., Rosen, S. T., Guitart, J., Duvic, M., Kim, Y. H., Dusza, S. W., & Kuzel, T. M. (2014). Results of an open-label multicenter phase 2 trial of lenalidomide monotherapy in refractory mycosis fungoides and Sézary syndrome. *Blood*, 123(8), 1159–1166. <https://doi.org/10.1182/blood-2013-09-525915>
- Ni, X., Jorgensen, J. L., Goswami, M., Challagundla, P., Decker, W. K., Kim, Y. H., & Duvic, M. A. (2015). Reduction of regulatory T cells by Mogamulizumab, a defucosylated anti-CC chemokine receptor 4 antibody, in patients with aggressive/refractory mycosis fungoides and Sézary syndrome. *Clinical cancer research : an official journal of the American Association for Cancer Research*, 21(2), 274–285. <https://doi.org/10.1158/1078-0432.CCR-14-0830>
- Parisi, L., Gini, E., Baci, D., Tremolati, M., Fanuli, M., Bassani, B., Farronato, G., Bruno, A., & Mortara, L. (2018). Macrophage Polarization in Chronic Inflammatory Diseases: Killers or Builders?. *Journal of immunology research*, 2018, 8917804. <https://doi.org/10.1155/2018/8917804>
- Wu, X., Schulte, B. C., Zhou, Y., Haribhai, D., Mackinnon, A. C., Plaza, J. A., Williams, C. B., & Hwang, S. T. (2014). Depletion of M2-like tumor-associated macrophages delays cutaneous T-cell lymphoma development in vivo. *The Journal of investigative dermatology*, 134(11), 2814–2822. <https://doi.org/10.1038/jid.2014.206>
- Furudate, S., Fujimura, T., Kakizaki, A., Kambayashi, Y., Asano, M., Watabe, A., & Aiba, S. (2016). The possible interaction between periostin expressed by cancer stroma and tumor-associated macrophages in developing mycosis fungoides. *Experimental dermatology*, 25(2), 107–112. <https://doi.org/10.1111/exd.12873>
- Murray, D., McMurray, J. L., Eldershaw, S., Pearce, H., Davies, N., Scarisbrick, J. J., & Moss, P. (2019). Progression of mycosis fungoides occurs through divergence of tumor immunophenotype by differential expression of HLA-DR. *Blood advances*, 3(4), 519–530. <https://doi.org/10.1182/bloodadvances.2018025114>
- Hsi, A. C., Lee, S. J., Rosman, I. S., Carson, K. R., Kelley, A., Viele, V., Pang, X., Musiek, A., & Schaffer, A. (2015). Expression of helper T cell master regulators in inflammatory dermatoses and primary cutaneous T-cell lymphomas: diagnostic implications. *Journal of the American Academy of Dermatology*, 72(1), 159–167. <https://doi.org/10.1016/j.jaad.2014.09.022>
- Miyashiro, D., Vivarelli, A. G., Gonçalves, F., Cury-Martins, J., & Sanches, J. A. (2020). Progression of mycosis fungoides after treatment with dupilumab: A case report. *Dermatologic therapy*, 33(6), e13880. <https://doi.org/10.1111/dth.13880>
- Wherry, E. J., & Kurachi, M. (2015). Molecular and cellular insights into T cell exhaustion. *Nature reviews. Immunology*, 15(8), 486–499. <https://doi.org/10.1038/nri3862>

- Zeng, Z., Wei, F., & Ren, X. (2020). Exhausted T cells and epigenetic status. *Cancer biology & medicine*, 17(4), 923–936. <https://doi.org/10.20892/j.issn.2095-3941.2020.0338>
- Scott, A. C., Dündar, F., Zumbo, P., Chandran, S. S., Klebanoff, C. A., Shakiba, M., Trivedi, P., Menocal, L., Appleby, H., Camara, S., Zamarin, D., Walther, T., Snyder, A., Femia, M. R., Comen, E. A., Wen, H. Y., Hellmann, M. D., Anandasabapathy, N., Liu, Y., Altorki, N. K., ... Schietinger, A. (2019). TOX is a critical regulator of tumour-specific T cell differentiation. *Nature*, 571(7764), 270–274. <https://doi.org/10.1038/s41586-019-1324-y>
- Tumino, N., Martini, S., Munari, E., Scordamaglia, F., Besi, F., Mariotti, F. R., Bogina, G., Mingari, M. C., Vacca, P., & Moretta, L. (2019). Presence of innate lymphoid cells in pleural effusions of primary and metastatic tumors: Functional analysis and expression of PD-1 receptor. *International journal of cancer*, 145(6), 1660–1668. <https://doi.org/10.1002/ijc.32262>
- Godal, R., Bachanova, V., Gleason, M., McCullar, V., Yun, G. H., Cooley, S., Verneris, M. R., McGlave, P. B., & Miller, J. S. (2010). Natural killer cell killing of acute myelogenous leukemia and acute lymphoblastic leukemia blasts by killer cell immunoglobulin-like receptor-negative natural killer cells after NKG2A and LIR-1 blockade. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*, 16(5), 612–621. <https://doi.org/10.1016/j.bbmt.2010.01.019>
- Sun, C., Xu, J., Huang, Q., Huang, M., Wen, H., Zhang, C., Wang, J., Song, J., Zheng, M., Sun, H., Wei, H., Xiao, W., Sun, R., & Tian, Z. (2016). High NKG2A expression contributes to NK cell exhaustion and predicts a poor prognosis of patients with liver cancer. *Oncoimmunology*, 6(1), e1264562. <https://doi.org/10.1080/2162402X.2016.1264562>
- Sako, N., Schiavon, V., Bounfour, T., Dessirier, V., Ortonne, N., Olive, D., Ram-Wolff, C., Michel, L., Sicard, H., Marie-Cardine, A., Bagot, M., Bensussan, A., & Schmitt, C. (2014). Membrane expression of NK receptors CD160 and CD158k contributes to delineate a unique CD4+ T-lymphocyte subset in normal and mycosis fungoides skin. *Cytometry. Part A : the journal of the International Society for Analytical Cytology*, 85(10), 869–882. <https://doi.org/10.1002/cyto.a.22512>
- Simon, S. C. S., Utikal, J., & Umansky, V. (2019). Opposing roles of eosinophils in cancer. *Cancer immunology, immunotherapy : CII*, 68(5), 823–833. <https://doi.org/10.1007/s00262-018-2255-4>
- Fredholm, S., Gjerdrum, L. M., Willerslev-Olsen, A., Petersen, D. L., Nielsen, I. Ø., Kauczok, C. S., Wobser, M., Ralfkiaer, U., Bonefeld, C. M., Wasik, M. A., Krejsgaard, T., Geisler, C., Ralfkiaer, E., Gniadecki, R., Woetmann, A., & Odum, N. (2014). STAT3 activation and infiltration of eosinophil granulocytes in mycosis fungoides. *Anticancer research*, 34(10), 5277–5286.
- Terada, T. (2013). Mycosis fungoides in plaque stage with pronounced eosinophilic infiltration, folliculotropism, and concomitant invasive squamous cell carcinoma. *International journal of clinical and experimental pathology*, 6(4), 749–756
- Aronovich, A., Moyal, L., Gorovitz, B., Amitay-Laish, I., Naveh, H. P., Forer, Y., Maron, L., Knaneh, J., Ad-El, D., Yaacobi, D., Barel, E., Erez, N., & Hodak, E. (2021). Cancer-Associated Fibroblasts in Mycosis Fungoides Promote Tumor Cell Migration

- and Drug Resistance through CXCL12/CXCR4. *The Journal of investigative dermatology*, 141(3), 619–627.e2. <https://doi.org/10.1016/j.jid.2020.06.034>
- Takahashi, N., Sugaya, M., Suga, H., Oka, T., Kawaguchi, M., Miyagaki, T., Fujita, H., & Sato, S. (2016). Thymic Stromal Chemokine TSLP Acts through Th2 Cytokine Production to Induce Cutaneous T-cell Lymphoma. *Cancer research*, 76(21), 6241–6252. <https://doi.org/10.1158/0008-5472.CAN-16-0992>
- Tuzova, M., Richmond, J., Wolpowitz, D., Curiel-Lewandrowski, C., Chaney, K., Kupper, T., & Cruikshank, W. (2015). CCR4+T cell recruitment to the skin in mycosis fungoides: potential contributions by thymic stromal lymphopoietin and interleukin-16. *Leukemia & lymphoma*, 56(2), 440–449. <https://doi.org/10.3109/10428194.2014.919634>
- Nakajima, R., Miyagaki, T., Hirakawa, M., Oka, T., Takahashi, N., Suga, H., Yoshizaki, A., Fujita, H., Asano, Y., Sugaya, M., & Sato, S. (2018). Interleukin-25 is involved in cutaneous T-cell lymphoma progression by establishing a T helper 2-dominant microenvironment. *The British journal of dermatology*, 178(6), 1373–1382. <https://doi.org/10.1111/bjd.16237>
- Geskin, L. J., Viragova, S., Stoltz, D. B., & Fuschiotti, P. (2015). Interleukin-13 is overexpressed in cutaneous T-cell lymphoma cells and regulates their proliferation. *Blood*, 125(18), 2798–2805. <https://doi.org/10.1182/blood-2014-07-590398>
- Vacca, A., Moretti, S., Ribatti, D., Pellegrino, A., Pimpinelli, N., Bianchi, B., Bonifazi, E., Ria, R., Serio, G., & Dammacco, F. (1997). Progression of mycosis fungoides is associated with changes in angiogenesis and expression of the matrix metalloproteinases 2 and 9. *European journal of cancer (Oxford, England : 1990)*, 33(10), 1685–1692. [https://doi.org/10.1016/s0959-8049\(97\)00186-x](https://doi.org/10.1016/s0959-8049(97)00186-x)
- Pileri, A., Agostinelli, C., Righi, S., Fuligni, F., Bacci, F., Sabattini, E., Patrizi, A., Pileri, S. A., & Piccaluga, P. P. (2015). Vascular endothelial growth factor A (VEGFA) expression in mycosis fungoides. *Histopathology*, 66(2), 173–181. <https://doi.org/10.1111/his.12445>
- Matsumoto, M., Roufail, S., Inder, R., Caesar, C., Karnezis, T., Shayan, R., Farnsworth, R. H., Sato, T., Achen, M. G., Mann, G. B., & Stacker, S. A. (2013). Signaling for lymphangiogenesis via VEGFR-3 is required for the early events of metastasis. *Clinical & experimental metastasis*, 30(6), 819–832. <https://doi.org/10.1007/s10585-013-9581-x>
- Lauenborg, B., Christensen, L., Ralfkiaer, U., Kopp, K. L., Jønson, L., Dabelsteen, S., Bonefeld, C. M., Geisler, C., Gjerdrum, L. M., Zhang, Q., Wasik, M. A., Ralfkiaer, E., Ødum, N., & Woetmann, A. (2015). Malignant T cells express lymphotoxin α and drive endothelial activation in cutaneous T cell lymphoma. *Oncotarget*, 6(17), 15235–15249. <https://doi.org/10.18632/oncotarget.3837>