

# Over-expression of Fatty Acid Synthase as a Potential Therapeutic Target in Classical Hodgkin Lymphoma

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## Introduction

Fatty acid synthase (FASN) is a multifunctional, homodimeric enzyme important in the de novo synthesis of fatty acids in the cytosol of animal cells. Recently, its overexpression has been reported in a variety of epithelial cancers including: breast, lung, ovary, thyroid, colon, and prostate, as well as hematological malignancies such as leukemia, multiple myeloma, and diffuse large B-cell lymphoma. FASN overexpression has been implicated in tumor cell proliferation, and subsequently, its downregulation has been associated with apoptosis in cancer cells. Its exact role is unclear, but it has been suggested that the increase in FASN enzyme activity may be associated with certain tyrosine kinases, such as hepatocyte growth factor receptor (HGF) encoded by *c-MET*, a proto-oncogene. Teofili et al. described the role of *c-Met*/HGF interaction in Hodgkin lymphoma as a pathway which sustains RS cells through their expression of alpha-4 and alpha-5 integrins of *c-Met* in a background of HGF-producing dendritic-reticulum cells. To this date, there have not been any studies which examine FASN overexpression in classical Hodgkin lymphoma (cHL). We examined 19 cases of cHL, 10 nodular sclerosing type and 9 mixed cellularity type, for their expression of FASN and S100, a marker for dendritic-reticulum cells.

## Methods

Nineteen cases of cHL, 10 nodular-sclerosing type and 9 mixed cellularity type, were retrospectively examined between 2008 and 2011. Immunohistochemical analysis of paraffin embedded tissue was used to detect FASN and S100 antigens. Protein expression was semi-quantified with brightfield microscopy by assessing the percentage of RS cells with cytoplasmic staining for FASN and the percentage of S100 positive interdigitating dendritic cells relative to the number of RS cells present. The percentages were graded on a 3 tiered scale as low, intermediate, and high. The results were then compared as a ratio to assess for correlation.

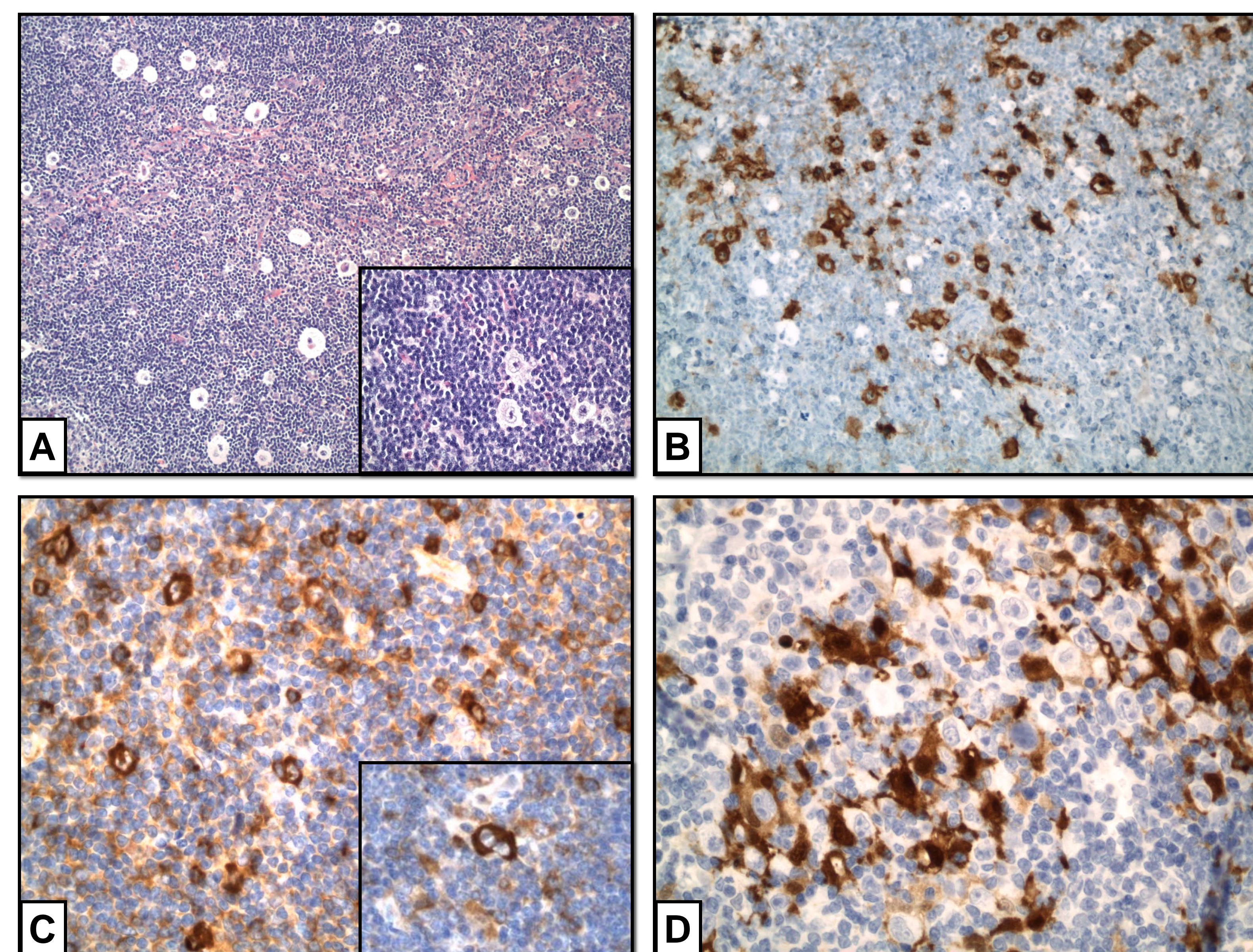


Figure 1. Classical Hodgkin lymphoma, mixed cellularity type. A. H&E, 4x and 40x. B. CD30, 20x. C. FASN, 40x. D. s100, 40x.

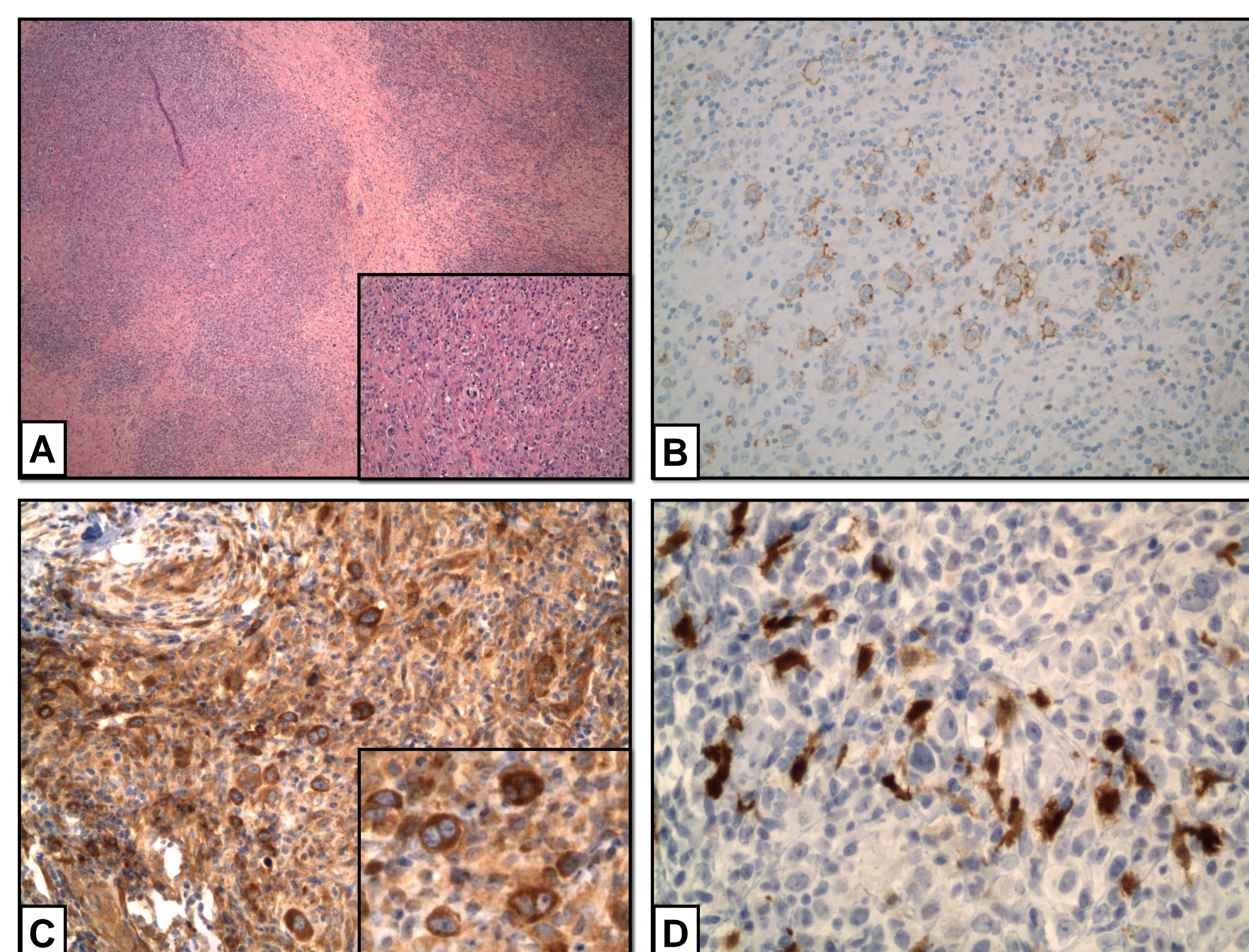


Figure 2. Classical Hodgkin lymphoma, nodular sclerosing type. A. H&E, 4x and 40x. B. CD30, 20x. C. FASN, 40x. D. s100, 40x.

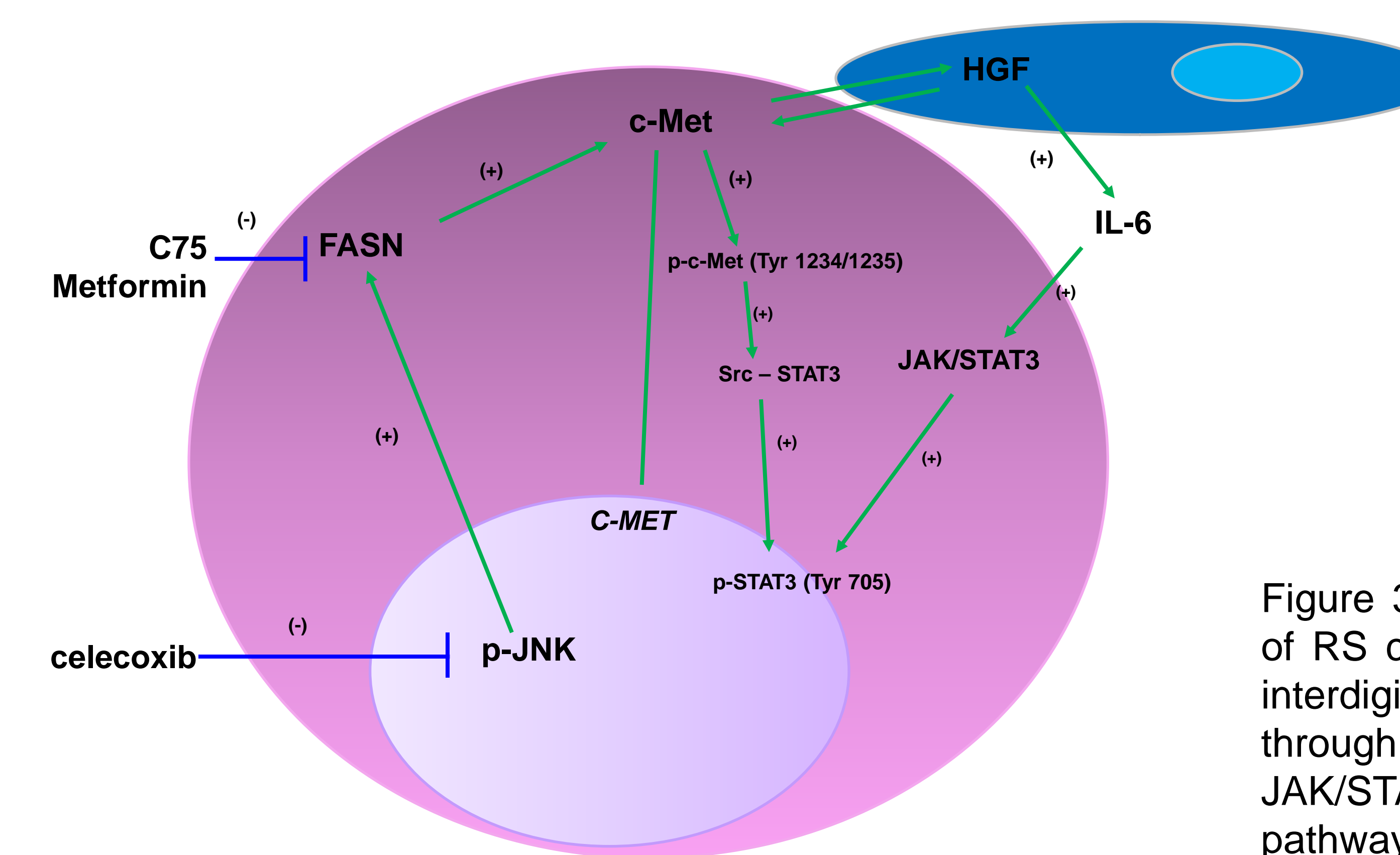


Figure 3. Schematic drawing of RS cells in relation to the interdigitating dendritic cells through the p-JNK, JAK/STAT3, and c-Met/HGF pathways.

## Results

Nine of ten (90%) cHL, NS type, and seven of nine (78%) cHL, MC type, cases showed FASN positive RS cells in a distribution which correlated with the number of RS cells present. Eight of ten (80%) cases of cHL, NS type, and seven of nine (78%) cHL, MC type, demonstrated an increase in the number of interdigitating cells relative to the number of RS cells present. When comparing the expression of FASN to the percentage of S100 interdigitating dendritic cells, we observed seven of ten (70%) cHL, NS type, and seven of nine (78%) cHL, MC type, cases had correlating increases in both FASN expression and increase in interdigitating dendritic cell proliferation.

## Discussion

- FASN overexpression in RS cells may play a significant role in tumor genesis in classical Hodgkin lymphoma through *c-Met*, as it has been previously described in diffuse large B cell lymphoma (DLBCL).

- Subsequently, FASN downregulation and *c-Met* suppression have been associated with apoptosis in many cancer cells implicating the use of new potential target therapies.

- Our results suggest the increase in FASN activity may be important to the malignant potential of RS cells.

- Further molecular studies should be conducted to demonstrate the direct role of fatty acid synthase in classical Hodgkin lymphoma.