ORIGINAL CONTRIBUTION

Structural Basis for How Biologic Medicines Bind their Targets in Psoriasis Therapy

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As biologic therapies become first line treatments for many inflammatory disorders, it becomes increasingly important for the practicing physician to be familiar with how these drugs function at the molecular level. This information is useful in making therapeutic decisions and helping patients understand their treatment options. It is critical to patient safety and clinical response that the molecular differences between these drugs inform prescribing practices. To this end, we present and analyze the available structural biology information about the biologics used in the treatment of psoriasis including inhibitors of tumor necrosis factor alpha (TNFα), interleukin-17 (IL-17), and interleukin-23 (IL-23). We describe and analyze the molecular surface character of known binding epitopes for medications in these classes, showing that significant differences exist in epitope location, hydrophobicity, and charge. Some of these differences can be correlated with clinical data, but our analysis ultimately points to the need for more structural information to allow for a better understanding of the structure-function relationship of biologic therapies.

INTRODUCTION

Biologics are a class of therapies increasingly being used in the treatment of psoriasis and other inflammatory diseases. Psoriasis is an immunologic disease that involves various cytokines in psoriatic lesions. Because cytokines and activated T cells promote the dysregulated growth of keratinocytes leading to plaques of erythematous, scaly skin, antibodies that target key cytokines in the inflammatory pathway are effective therapeutics for this disease. The three main classes of biologics used in the treatment of psoriasis are inhibitors of tumor necrosis factor alpha (TNFα), interleukin-17 (IL-17), and interleukin-23 (IL-23). As new biologics emerge with similar or identical targets, explanations for differences in clinical effect require an increasingly nuanced understanding of mechanisms of action. We believe that knowledge of the structural biology of drug binding provides the clinician with a perspective that allows for more informed decisions about drug prescribing practices, especially when switching patients from one biologic drug to another. While clinicians should follow existing Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics [1], the authors of these guide-

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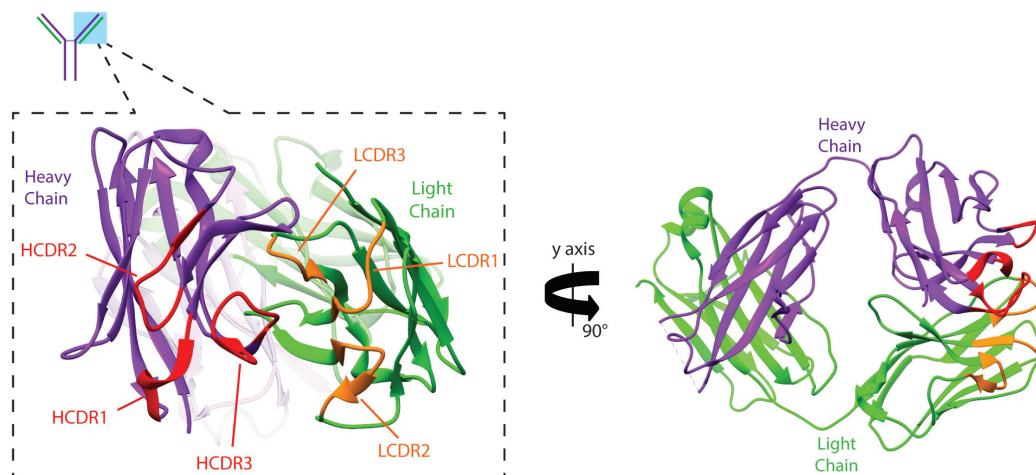
Figure 1. **Structure of a Fab Fragment and its CDR loops**. Illustrative Fab fragment (upper left) with zoomed-in view of an x-ray crystal structure of Fab fragment of adalimumab (heavy chain purple, light chain green). The complement determining region (CDR) locations (red and orange) are highlighted. The CDR loops determine the epitope bound by the antibody.

Table 1. Crystal structures used in this study.

Protein or Protein Complex	PDB ID	Reference
TNFα	1TNF	[24]
TNFR2-TNFα	3ALQ	[7]
Adalimumab-TNFα	3WD5	[8]
Certolizumab-TNFα	5WUX	[9]
Infliximab-TNFα	4G3Y	[10]
Golimumab-TNFα	5YOY	[11]
IL-17A	4HR9	[14]
IL-17RA-IL-17A	4HSA	[14]
IL-17F	1JPY	[15]
IL-23	5MXA	[19]
IL-23RA-IL-23	5MZV	[19]
Ustekinumab-IL-12p40	3MHX	[20]

lines emphasize that there is not enough data to make recommendations about switching therapies. An analysis of the molecular differences between drugs within and across biologic drug classes helps fill this knowledge gap. Additionally, information about molecular structure is invaluable to scientists in the drug development process.

Most structural information about the action of biologics comes from x-ray crystal structures of Fab (fragment antigen binding) fragments bound to their cytokine target. Since biologics are antibody molecules, they have unique Fab fragments while sharing a common immunoglobulin structure (with a few exceptions that are discussed later). Within the Fab fragments, CDRs (complement-determining regions) are the main component

involved in binding and they determine the antibody's specificity to its target. The light and heavy chains in the Fab region of an antibody each have three CDRs composed of loops (Figure 1) [2].

Despite sharing a similar general structure, biologics bind to a variety of cytokines. Analysis of those cytokine structures, particularly the epitopes where the drugs bind, allows for the formation of hypotheses about drug action. Furthermore, comparison of receptor and drug binding sites provides insights not otherwise apparent without a structural perspective.

MATERIALS AND METHODS

Crystal structures listed in Table 1 were obtained from the Protein Data Bank (PDB) and analyzed for binding surface location, hydrophobicity, and charge using UCSF Chimera (Computer Graphics Laboratory, University of California, San Francisco) [3] and PISA (Protein Interfaces, Surfaces and Assemblies' service) [4]. Overall binding surface character pie charts shown in Figures 3, 6, and 7 were calculated by tabulating all solvent accessible surface area of each residue in the epitope categorized as acidic (D, E), basic (R, K), polar (Q, N, H, S, T, Y, C, G), or hydrophobic (A, I, L, F, V, P, M, W).

RESULTS AND DISCUSSION

TNFα

The TNFα molecule is expressed on the cell surface as transmembrane TNFα (tmTNFα), which is cleaved by TNF alpha converting enzyme (TACE) into soluble
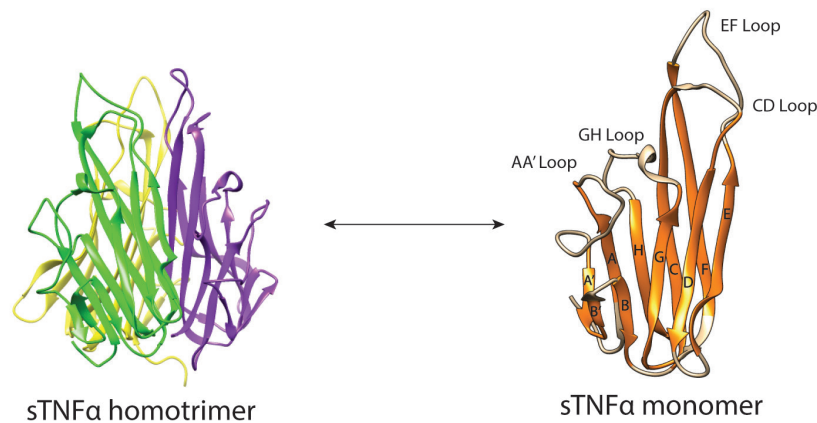
Figure 2. **TNFα structure**. X-ray crystal structure of the sTNFα (soluble TNF alpha) homotrimer and monomer [24]. sTNFα is produced by cleavage from transmembrane TNF alpha (tmTNFα). An equilibrium exists between the homotrimer and monomer. Specific loop regions and beta strands are labeled on the monomer, as these are important for describing where TNFα inhibitors bind.

TNFα (sTNFα). Both tmTNFα and sTNFα have biological activity, and the biologically active unit of both forms is a homotrimer (Figure 2) [2]. An equilibrium exists between the monomer and trimer forms, and slow monomer exchange of sTNFα has been observed [5]. The main receptors for TNFα are TNFR1 and TNFR2.

Currently, five TNFα inhibitors are approved for clinical use: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab. All five drugs directly bind TNFα to produce their inhibitory effect; the binding of sTNFα neutralizes the cytokine, while in some cases the binding of tmTNFα can trigger antibody-dependent cell cytotoxicity (ADCC) [6]. Adalimumab, golimumab, and infliximab are IgG antibodies. Etanercept is comprised of two TNFR2 receptors attached to a fragment crystallizable (Fc) region, and certolizumab pegol is a PEGylated (modified with polyethylene glycol) Fab and lacks a Fc region. The structure of the TNFR2-TNFα complex is representative of the etanercept-TNFα interface [7], while crystal structures of Fab-TNFα complexes are available for the remaining 4 TNFα inhibitors [8-11].

As a homotrimer, the TNFα molecule contains three of each epitope shown in Figure 3. Except for etanercept, which binds the TNFα trimer in a 1:1 stoichiometry (both TNFR2 molecules on etanercept bind one TNFα trimer), the other four drug Fabs bind in a 3:1 stoichiometry. The infliximab and golimumab epitope locations are similar, primarily involving the loop regions of the TNFα molecule (Figure 3c,d), while certolizumab, adalimumab, and etanercept bind residues located more in the beta sheet strands (Figure 3a,b,e). Neither certolizumab nor etanercept bind to the EF loop; this region is thus not stabilized by antibody binding in the Fab-TNFα structure, and the EF loop is missing in the structures for these two drugs.

The etanercept and adalimumab epitopes span two TNFα monomers, while the certolizumab, golimumab, and infliximab epitopes are contained on one subunit. Of the five drugs, golimumab overlaps the least with the TNFR2 binding site; only one residue, a glutamine on the CD loop, is common to the binding sites of both TNFR2 and golimumab (Figure 3f).

To better understand TNFα inhibitor drug binding sites, we analyzed the TNFα solvent-accessible molecular surface and characterized its hydrophobicity and charge distribution for each drug epitope (Figure 3). A polar solvent-accessible surface area (SASA) of about 50% was found in all the binding epitopes. The etanercept and adalimumab epitopes have the most significant hydrophobic surface areas (>20% SASA), while the certolizumab, golimumab, and infliximab epitopes are less hydrophobic (10% SASA or less). The charge potential of the molecular surfaces of the adalimumab, golimumab, and infliximab binding sites on TNFα are predominantly negative (acidic) due to a large proportion of acidic surface area. The certolizumab binding surface on TNFα appears mostly neutral due to roughly equal surface area contributed by acidic and basic residues, resulting in a net neutral character. The etanercept binding site also has an overall neutral charge but differs due to the presence of fewer charged residues.

Clinical Relevance

Knowledge of the differences in epitope location and surface chemistries is particularly useful in choosing a second-line drug following failure of a previously attempted therapy. Success is most likely when switching to a drug that is sufficiently different from one that has already proven ineffective. The number of TNFα sub-
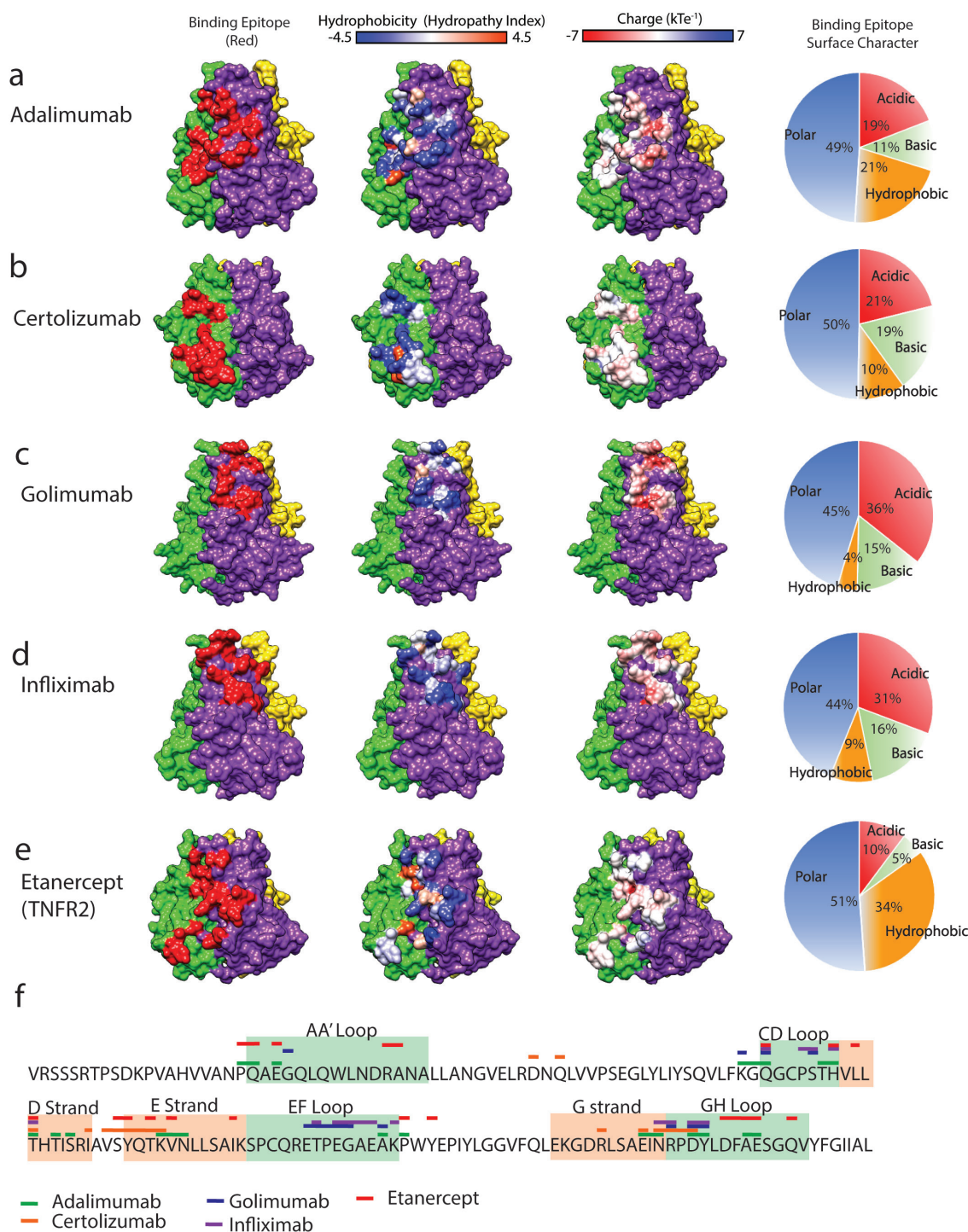
Figure 3. **Characterization of the TNFα binding epitopes for TNFα inhibitors and receptor**. Binding epitope location (column 1), hydrophobicity potential (column 2) and electrostatic/charge potential (column 3) mapped onto the sTNFα trimer molecular surface (monomers colored green, purple, and yellow) for (**a**) adalimumab, (**b**) certolizumab, (**c**) golimumab, (**d**) infliximab, and (**e**) etanercept. These were determined from the drug-TNFα complex crystal structure for each drug (the crystal structure of the TNFR2-TNFα complex was used for etanercept). The overall epitope surface character (polar, acidic, basic, and hydrophobic surface area) is shown as a pie chart in column 4. (**f**) TNFα inhibitor epitopes shown as lines above each binding residue in the TNFα protein sequence.
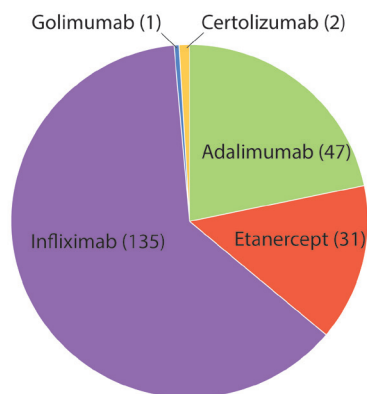
Figure 4. **TNFα-induced psoriasis**. Number of cases of TNFα inhibitor-induced psoriasis found in the literature for each drug by a recent review [12].

units in the homotrimer that are bound by a single drug molecule is a particularly relevant structural feature, as binding of multiple subunits by adalimumab and etanercept molecules results in stabilization of the TNFα homotrimer, thus reducing monomer exchange. Infliximab has also been shown to inhibit monomer exchange despite only binding a single subunit for reasons that are not fully understood [5]. Trimer stabilization has been shown to prolong residual TNFα bioactivity *in vitro* [5]. This effect may increase the half-life of the TNFα trimer and thus potentiate the inflammatory effect of the cytokine and lead to adverse effects. For example, it has been noted that a paradoxical effect of TNFα inhibitor therapy in some patients is the onset of psoriasis. TNFα inhibitor-induced psoriasis has been reported with infliximab, etanercept, and adalimumab significantly more than for certolizumab and golimumab [12] (Figure 4). Switching to a different TNFα inhibitor is less effective than discontinuing therapy in these cases. One possible explanation is that switching from one trimer-stabilizing drug to another fails to solve the problem, and only when switching to a non-stabilizer does the issue resolve. There is not enough data in the literature currently, however, to test this hypothesis.

The overall structure of the drugs is also a relevant consideration as it impacts pharmacokinetic properties and clinical efficacy. Certolizumab pegol, for example, is unique due to the presence of covalently linked polyethylene glycol, which impacts the drug's overall hydrophobicity and surface charge, increases drug half-life, and decreases immunogenicity [13]. Furthermore, while all five TNFα inhibitors are known to bind tmTNFα, adalimumab, infliximab, golimumab, and etanercept trigger ADCC of TNFα-expressing cells while certolizumab does not [6]. This observation is in line with the structures of these antibodies, as the four ADCC-inducing drugs have an Fc region which can be recognized by the Fc receptors on inflammatory cells to trigger ADCC, while certolizumab lacks an Fc region and thus does not recruit the necessary immune response against tmTNFα-expressing cells. While this distinction is most pertinent to the treatment of granulomatous disorders [6] and does not correlate with efficacy in the treatment of psoriasis, understanding this difference in mechanism of action may lead to insights into adverse effects and other subtleties that would have implications for all patients being treated with these drugs.

IL-17

There are six isoforms of IL-17, ranging from IL-17A to IL-17F, and there are five IL-17 receptors (IL-17Rs), ranging from IL-17RA to IL-17RE. IL-17A and IL-17F share the greatest homology (50%) and are the two most relevant isoforms to clinical IL-17 inhibition. Unlike the trimeric TNFα molecule, both IL-17A and IL-17F are dimers. They have been characterized as homodimers consisting of two identical molecules (Figure 5a,b). They can also exist as an IL-17A/IL-17F heterodimer, although the biologic role of this heterodimer is unclear [14]. IL-17A and IL-17F signal via the same two receptors, IL-17RA and IL-17RC. The IL-17 dimer binds first to IL-17RA, which induces a conformational change in the IL-17 molecule to allow binding of IL-17RC. IL-17A has a significantly greater affinity than IL-17F for IL-17RA [14].

The IL-17 inhibitors currently in clinical use include ixekizumab, secukinumab, and brodalumab. Ixekizumab and secukinumab target IL-17A, while brodalumab targets the receptor IL-17RA. Considerably less structural information is available for the IL-17 inhibitors compared to the TNFα inhibitors; crystallographic information exists for IL-17A [14], IL-17F [15], and the IL-17A-IL-17RA complex [14], but there are no available structures of IL-17-drug complexes. Available information about drug binding includes the ixekizumab epitope derived from hydrogen-deuterium mass spectrometry [16] and the secukinumab epitope, which has been publicly disclosed [17]. There is no structural information available for brodalumab.

Analysis of the IL-17RA, secukinumab, and ixekizumab binding sites on the IL-17A molecule (Figure 6) shows that almost the entirety of the secukinumab epitope overlaps with the IL-17RA binding surface, while a considerably larger portion of the ixekizumab epitope lies outside of the receptor binding region. The secukinumab epitope covers both molecules in the IL-17A dimer, while ixekizumab only binds one molecule in the dimer. Although the secukinumab epitope spans both subunits, it is restricted to a smaller (49-55%) surface area (1830 Å^2) compared to the binding sites of IL-17RA (3330 Å^2) and ixekizumab (3720 Å^2).
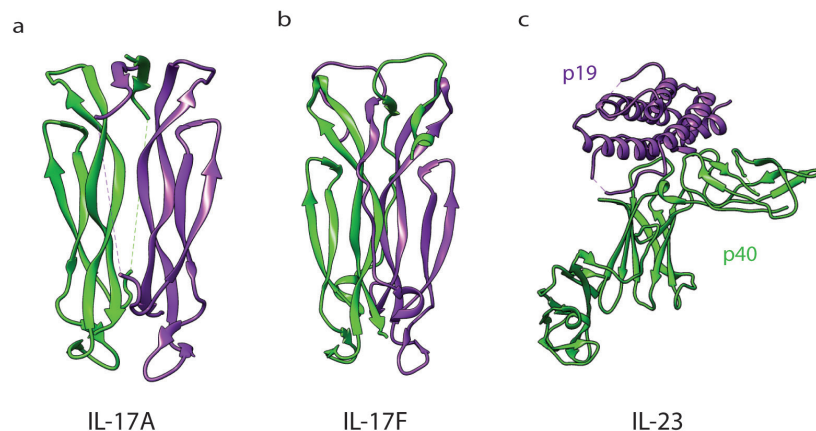
Figure 5. **IL-17 and IL-23 structures**. X-ray crystal structures of the (**a**) IL-17A, (**b**) IL-17F, and (**c**) IL-23 dimers. The two subunits in each dimer are colored purple and green. Dotted lines indicate structural elements missing from the crystal structures (due to protein flexibility and motion within the crystal lattice).

Analysis of the solvent-accessible molecular surface of the IL-17RA and secukinumab epitopes on IL-17A shows that both have significant polar and hydrophobic surface character, while the ixekizumab binding site has primarily polar character. In contrast to the TNFα molecule, which binds via primarily acidic interfaces, the IL-17A binding surfaces are more basic (positively charged). The ixekizumab epitope has the highest basic SASA (19%) with a prominent basic patch visible near the dimer interface.

Clinical Relevance

Because both faces of the IL-17 dimer are required to bind two unique receptors, IL-17RA and IL-17RC, binding of one drug molecule is theoretically sufficient to block biological activity, unlike the case of TNFα in which binding of a TNFα trimer by one drug molecule may still leave enough space for receptor binding. It is not known whether one or two secukinumab/ixekizumab molecules can bind a single IL-17A molecule. Given that IL-17RC binds IL-17A after an IL-17RA-induced conformational change, it is possible that a conformational change occurs after drug binding that prevents a second drug molecule from associating with the opposite face.

There is a major need for structural studies of IL-17 inhibitors. The possibility of receptor interaction with partially inhibited IL-17 is a consideration that requires structural investigation. Structural validation of biochemically determined epitopes is also important to fully elucidate the binding mechanism of these drugs. Interestingly, a biologic drug in clinical trials, bimekizumab, targets both IL-17A and IL-17F [18]; crystallographic information comparing the binding of bimekizumab, secukinumab, and ixekizumab to IL-17A would likely provide

insights into binding specificity, which would be particularly valuable for drug development. Another useful structure would be the brodalumab-IL-17RA complex, which would provide mechanistic information about drug function.

IL-23

The IL-23 cytokine differs from the homomeric TNFα and IL-17 molecules because it is a heterodimer made up of the p19 and p40 subunits (Figure 5c). The p19 subunit is a helical subunit unique to IL-23, whereas the p40 subunit is common to several cytokines including IL-12. Like IL-17, IL-23 function requires interaction with two different receptors; IL-23 first binds IL-23R, which then primes the cytokine to bind IL-23Rβ1 (also known as IL-12Rβ1) [19].

IL-23 inhibitors approved for clinical use include tildrakizumab, risankizumab, and guselkumab, all of which are antibodies that specifically target IL-23, as well as ustekinumab, which targets both IL-12 and IL-23. Structures exist for the IL-23-IL-23R complex [19] as well as the p40-ustekinumab complex [20], but no structural information is available for IL-23Rβ1 or the targeted IL-23 inhibitors.

The binding sites of IL-23R and ustekinumab on the IL-23 molecule are shown in Figure 7a. As expected, the p19 subunit greatly contributes to IL-23R binding, while the p40 subunit contributes a minor amount of binding area. Ustekinumab only binds the p40 subunit, which explains its ability to bind both IL-12 and IL-23. The molecular surfaces of the IL-23R and ustekinumab binding sites have similarly high hydrophobic surface areas (> 30% SASA) forming several hydrophobic patches (Figure 7b,d). The IL-23 binding surfaces notably differ
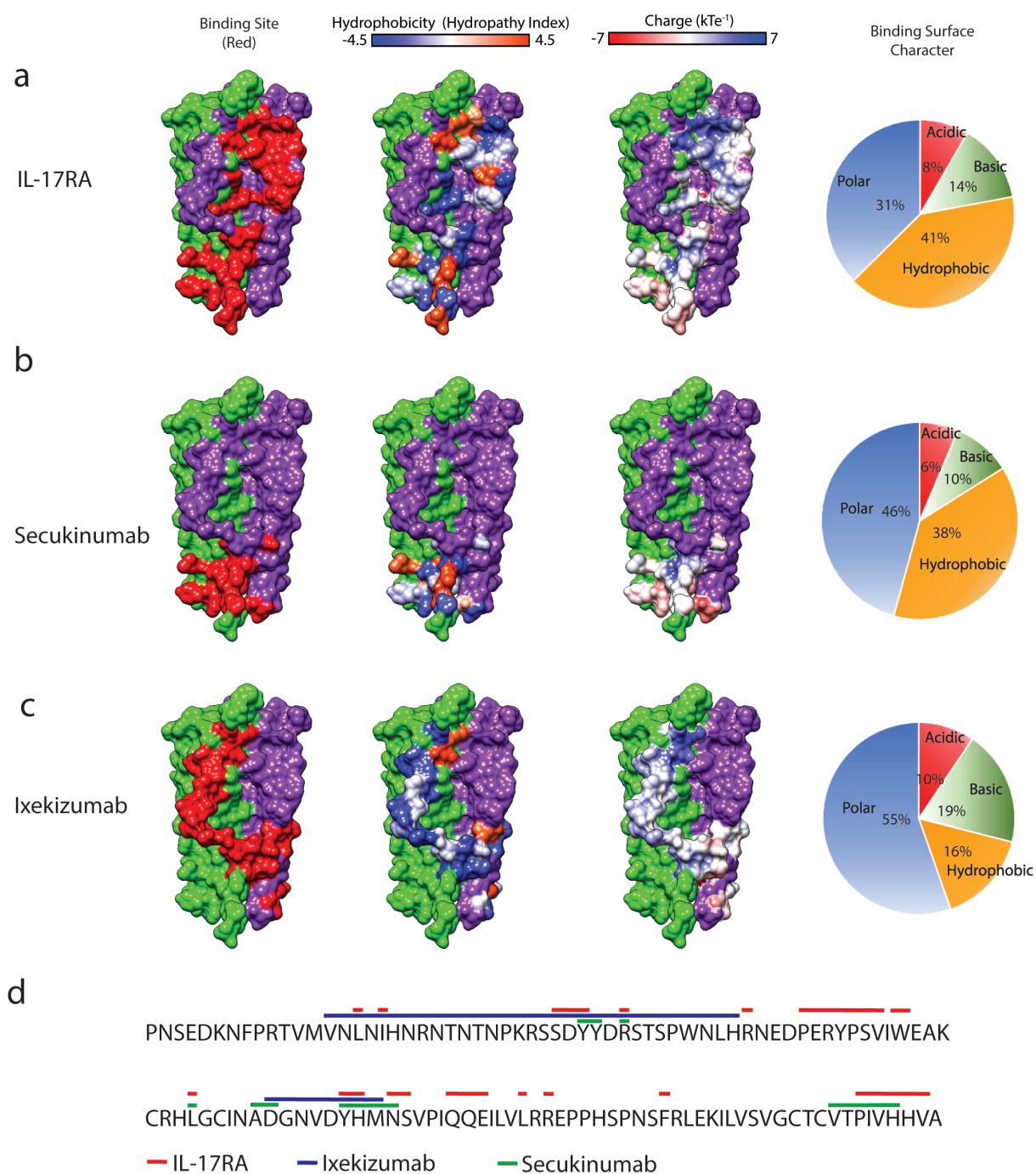
Figure 6. **Characterization of the IL-17A binding epitopes for IL-17A inhibitors and receptor**. Binding epitope location (column 1), hydrophobicity potential (column 2) and electrostatic/charge potential (column 3) mapped onto the IL-17A dimer molecular surface (the two monomers are colored purple and green) for (**a**) IL-17RA, determined by the IL-17A-IL-17RA crystal structure, (**b**) secukinumab, based on the disclosed binding epitope, and (c) ixekizumab, determined by hydrogen-deuterium mass spectroscopy. The overall epitope surface character (polar, acidic, basic, and hydrophobic surface area) is shown as a pie chart in column 4. (**d**) Residues involved in binding of IL-17RA, secukinumab, and ixekizumab shown as lines above the IL-17A amino acid sequence.
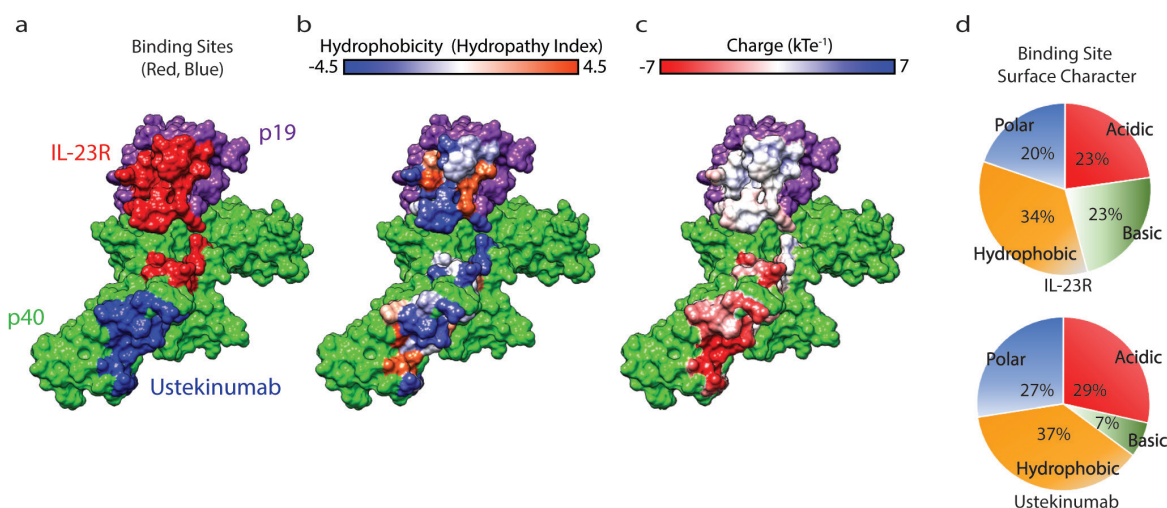
Figure 7. **Characterization of the IL-23 binding epitopes for IL-23R and Ustekinumab**. (**a**) Binding epitope location of IL-23R (red) and ustekinumab (blue) on the IL-23 molecular surface determined by x-ray crystallography. The p19 subunit is colored purple and the p40 subunit is colored green. (**b**) Hydrophobicity potential of the IL-23 binding epitope for IL-23R and ustekinumab mapped onto the IL-23 molecular surface. (**c**) Electrostatic/charge potential of the IL-23 binding epitope for IL-23R and ustekinumab mapped onto the IL-23 molecular surface. (**d**) The overall epitope surface character (polar, acidic, basic, and hydrophobic surface area) of the IL-23R (top) and ustekinumab (bottom) binding sites.

from those of TNFα and IL-17A because the IL-23 surface has large areas of charged residues. Almost 50% of the IL-23R binding surface is charged (either acidic or basic), while 36% of the ustekinumab binding surface is charged. A key difference, however, is that the IL-23R binding site has equal basic and acidic character, resulting in a net neutral charge, while the ustekinumab binding site is strongly acidic (Figure 7c).

Clinical Relevance

There is no overlap between the ustekinumab and IL-23R binding sites, suggesting that blocking of IL-23Rβ1 binding is the key mechanism of IL-23 inhibition by ustekinumab. This represents an important difference between ustekinumab and the specific IL-23 inhibitors, as the latter group necessarily binds at least in part to the p19 subunit to achieve specificity for its target. As a result, tildrakizumab, risankizumab, and guselkumab are likely to prevent IL-23R binding. This difference is significant because IL-23 containing inactivated p40 has been shown to have IL-23R mediated, IL-23Rβ1-independent biologic activity [21]. Thus, the lower clinical response rate seen in ustekinumab compared to targeted IL-23 antagonists [22] may be related to the ability of the ustekinumab-IL-23 complex to induce an inflammatory response via interaction with IL-23R in some patients.

CONCLUSION

Structural information about drug and receptor complexes with cytokines give insight into biologic therapy mechanisms of action and have implications for clinical practice. Analysis of the drug-binding epitopes of TNFα, IL-17A, and IL-23 show differences in surface location, charge, and hydrophobicity. The surface characteristics of each epitope reflect the way a complementary antibody recognizes and interacts with its target. Differences in these epitopes thus represent subtle variations in mechanism of action. Some of these differences can be correlated with drug efficacy and adverse effects. However, this research is limited by a need for more clinical data to correlate with our analysis as well as more structural studies of biologics, especially of IL-17 and targeted IL-23 inhibitors. Structures of these drugs bound to their targets would allow for comparison between drugs within each biologic class as well as across different classes of biologic drugs. Hypotheses derived from these studies are likely to impact clinical practice as well as future drug development because they address the structure-function relationship of the therapeutics. The known impact of structure on drug immunogenicity [23], for example, could be further explored with the molecular structures of drugs to compare with clinically identified rates of anti-drug antibody formation. Future drugs could then be optimized to decrease immunogenicity based on this data. For the clinician, this information increases the ability to make

evidence-based decisions. There are implications for insurance company policies, which sometimes require the trial of multiple drugs within a class before switching biologic therapies. From the patient perspective, having a physician that fully understands how biologics work will empower the patient-doctor relationship and increase confidence in decisions made by the prescriber and the patient.

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